Resting and Exercise Cardiovascular Magnetic Resonance Imaging for the Assessment of Mitral Regurgitation

Dr Thomas Paul Craven MBChB

Submitted in accordance with the requirements for the degree of

Doctor of Medicine (MD)

The University of Leeds

Faculty of Medicine and Health

Leeds Institute of Cardiovascular and Metabolic Medicine

January 2021

Intellectual Property and Publication Statements

The candidate confirms that the work submitted is his own, except where work which has formed part of jointly-authored publications has been included. The contribution of the candidate and the other authors to this work has been explicitly indicated below. The candidate confirms that appropriate credit has been given within the thesis where reference has been made to the work of others. This copy has been supplied on the understanding that it is copyright material and that no quotation from the thesis may be published without proper acknowledgement. The right of Thomas Paul Craven to be identified as Author of this work has been asserted by Thomas Paul Craven in accordance with the Copyright, Designs and Patents Act 1988.

Chapter 1

Publication: Craven TP, Tsao CW, La Gerche A, Simonetti OP, Greenwood JP. Exercise cardiovascular magnetic resonance: development, current utility and future applications: J Cardiovasc Magnet Reson, 22(1):65. https ://doi.org/10.1186/s1296 8-020-00652 –w.

Authorship: TC led the design, performed the literature search and drafted the manuscript. CT, AG and OS reviewed and revised the manuscript; whilst JG contributed to the conception, offered intellectual input and approved the final version of manuscript.

Chapter 2

Publication: Craven TP, Jex N, Chew PG, Higgins DM, Bissell MM, Brown LAE, Saunderson CED, Das A, Chowdhary A, Dall'Armellina A, Levelt E, Swoboda PP, Plein S & Greenwood JP. Exercise cardiovascular magnetic resonance: feasibility and development of biventricular function and great vessel flow assessment, during continuous exercise accelerated by Compressed SENSE: preliminary results in healthy volunteers. The international journal of cardiovascular imaging. 2020. (in press) DOI 10.1007/s10554-020-02044-8.

Authorship: TC performed the conception and design of study, recruitment, acquisition of data, data analysis and interpretation and drafted the manuscript. PC, DH, MB, PS and JG contributed to the conception and design of the study; whilst DH, MB, and PS were involved in the acquisition of data and NJ the analysis of data (inter-observer analysis). All authors reviewed and revised the manuscript. DH, PS, SP and JP offered intellectual input. All authors read and approved the final manuscript.

Chapter 4

Publication: Craven TP, Chew PG, Dobson LE, Gorecka M, Brown LAE, Saunderson CED, Das A, Chowdhary A, Jex N, Higgins DM, Dall'Armellina A, Levelt E, Swoboda PP, Plein S & Greenwood JP, Cardiac reverse remodelling for degenerative mitral regurgitation: mitral valve replacement vs. mitral valve repair [under-review with Circulation].

Authorship: TC recruited patients, performed data acquisition and analysis, its interpretation and drafted the manuscript. LD and JG contributed to the conception and design of the study; whilst LD and PC were also involved in patient recruitment and acquisition of data. LB, CS, AS, AC, NJ, DH, ED and EL reviewed and revised the manuscript. SP and JP offered intellectual input, all authors reviewed and approved final version of manuscript.

Publications arising from this work:

Papers:

1. Craven TP, Tsao CW, La Gerche A, Simonetti OP, Greenwood JP. Exercise cardiovascular magnetic resonance: development, current utility and future applications: J Cardiovasc Magnet Reson, 22(1):65. https ://doi.org/10.1186/s1296 8-020-00652 –w. Also presented at the SCMR journal club on the 11/11/2020
2. Craven TP, Jex N, Chew PG, Higgins DM, Bissell MM, Brown LAE, Saunderson CED, Das A, Chowdhary A, Dall'Armellina A, Levelt E, Swoboda PP, Plein S & Greenwood JP. Exercise cardiovascular magnetic resonance: feasibility and development of biventricular function and great vessel flow assessment, during continuous exercise accelerated by Compressed SENSE: preliminary results in healthy volunteers. The international journal of cardiovascular imaging. 2020. DOI 10.1007/s10554-020-02044-8

Abstracts:

1. Craven TP, Jex N, Higgins DM, Bissell MM, Brown LAE, Saunderson CED, Das A, Chowdhary A, Dall'Armellina A, Levelt E, Swoboda PP, Plein S & Greenwood JP, The development and assessment of a free breathing Compressed SENSE protocol assessing biventricular volumes and great vessel flow, Poster presentation at SCMR conference, Orlando Florida, February 2020.
2. Craven TP, Jex N, Chew PG, Higgins DM, Bissell MM, Brown LAE, Saunderson CED, Das A, Chowdhary A, Dall'Armellina A, Levelt E, Swoboda PP, Plein S & Greenwood JP, Feasibility and potential clinical utility of biventricular function, aortic an pulmonary flow assessment using Compressed SENSE during continuous Exercise Cardiovascular Magnetic Resonance (Ex-CMR). Accepted for poster presentation at BCS,

Manchester, June 2020, conference cancelled due to COVID-19 pandemic, abstract published in Heart. Heart 2020;106(Suppl 2):A87-A88

3. Craven TP, Chew PG, Dobson LE, Brown LAE, Saunderson CED, Das A, Chowdhary A, Jex N, Higgins DM, Dall'Armellina A, Levelt E, Swoboda PP, Plein S & Greenwood JP, Cardiac reverse remodelling for degenerative mitral regurgitation: mitral valve replacement vs. mitral valve repair [pending]. Accepted for poster presentation at the SCMR 2021 conference.

Acknowledgments

This work would not have been possible without the contribution and support of others. I would like to express my gratitude to my supervisors, Professor John P Greenwood and Professor Sven Plein. Their academic guidance has been invaluable and it has been a privilege to have been part of the University of Leeds CMR team. Particular thanks go to Professor Greenwood without whom the publication of this thesis would never have been possible. I am grateful to the research nurses Fiona Richards, Hannah Newman and Petra Bijsterveld for ensuring smooth running of studies. I want to give special thanks go to Fiona, for her hard work and assistance in patient recruitment.

I would like to thank my fellow colleagues: Drs Brown, Saunderson, Das, Chowdhury, Jain, Jex, Thirunavukarasu & Sharrack for their assistance and friendship over the past 2 years. I wish to extend special thanks to my predecessors Dr Laura Dobson and Dr Pei Gee Chew and acknowledge their efforts in initial recruitment and data acquisition of patients in the studies presented in Chapters 4 & 5. I want to further thank Dr Chew for her guidance and organisational skills that made the handover and transition period seamless. I wish to give special thanks to Dr Nicholas Jex for his time and effort performing intra-observer analysis in both Exercise CMR studies (Chapters 2 & 3).

Special thanks are due to the excellent radiographers (Margaret, Lisa, Gavin, Julian & Sophie) for their technical knowledge, scanning of patients and assistance and for being a joy to work with. I am also grateful to the assistants Debbie and Claire for their help.

The greatest thanks go to the patients who invested their time to participate in these research projects, which helps to increase our understanding in this field and will hopefully lead to improvements in patient care.

Last but not least, I want to thank my wife, Lauren, for her understanding and unwavering support through the ups and downs of my research and to my children Oliver and Amelie for constantly making me smile throughout.

This research has been carried out by a team which has included all the names stated above. My own contributions, fully and explicitly indicated in the thesis, have been in the form of study design, patient recruitment and scanning, data collection, data analysis and manuscript preparation. The contributions of other members of the group are as stated above.

Thesis abstract

Background

Mitral regurgitation (MR) is a heterogeneous disease requiring accurate investigations to guide optimal management. Cardiovascular magnetic resonance (CMR) provides reference standard biventricular assessment and highly reproducible MR quantification. Exercise-CMR (Ex-CMR) combines CMR with physiological stress; further development may allow comprehensive MR assessment. Therefore CMR is ideal to assist clinical decision making and assess research outcomes.

Aims

The thesis aims were to: **1)** Develop and validate an Ex-CMR protocol assessing biventricular volumes and great vessel flow in healthy volunteers, **2)** Evaluate the validated Ex-CMR protocol in primary MR patients, **3)** Compare cardiac reverse remodelling and residual MR post mitral valve repair (MVr) vs replacement (MVR) in primary MR patients **4)** Assess cardiac reverse remodelling after percutaneous mitral valve intervention for primary MR.

Methods

1) Free-breathing, respiratory navigated Compressed-SENSE short-axis cines and aortic/pulmonary phase contrast magnetic resonance sequences were validated against clinical sequences at rest and used during Ex-CMR in 12 healthy volunteers, **2)** 10 primary MR patients underwent the validated Ex-CMR protocol, **3)** Of 83 moderate-severe primary MR patients, 72 (30 MVr, 22 MVR, 20 controls) completed CMR imaging at baseline and 6 months after mitral surgery or observation (control group). **4)** Of 11 primary MR patients, 10 completed CMR imaging at baseline and 6-months after percutaneous intervention.

Findings

1) Biventricular volumes and great vessel flow assessment during continuous supine Ex-CMR is feasible in healthy volunteers using the Compressed-SENSE

Ex-CMR protocol, demonstrating good/excellent intra/inter-observer reproducibility, **2)** The validated Ex-CMR protocol is feasible in asymptomatic primary MR patients demonstrating effective forward left ventricular ejection fraction is augmented by decreases in MR, **3)** MVR results in comparable cardiac reverse remodelling to MVr with lower residual quantitated MR and better right ventricular ejection fraction (compared with controls) **4)** In primary MR, percutaneous valve intervention results in MR reduction and positive left-ventricular reverse remodelling.

Table of Contents

List of Figures

List of Tables

List of Equations

List of Abbreviations

$\%HR_{max}$	Percentage of Maximal Heart Rate
%HRR	Percentage of Maximal Heart Rate by Heart Rate Reserve Method
$\%VO_{2max}$	Percentage of Maximal Oxygen Uptake
$\%VO_2R$	Percentage of Maximal Oxygen Reserve
^{31P}MRS	Phosphorus Magnetic Resonance Spectroscopy
6MWT	6-minute walk test
AF	Atrial Fibrillation
AHA	American Heart Association
AMVL	Anterior Mitral Valve Leaflet
ANOVA	Analysis of Variance
AR	Aortic Regurgitation
ASE	American Society of Echocardiography
BH	Breath Held
BMI	Body Mass Index
BP	Blood Pressure
BSA	Body Surface Area
bSSFP	balanced Steady State Free Precision
CABG	Coronary Artery Bypass Grafting
CAD	Coronary Artery Disease
CBT	Cardiopulmonary Bypass Time
CCT	Cross Clamp Time
CMR	Cardiovascular Magnetic Resonance
CPET	Cardiopulmonary Exercise Testing
CS3	Compressed SENSE 3
CS6	Compressed SENSE 6
CSA	Cross Sectional Area
C-SENSE	Compressed SENSE
CV	Coefficient of Variance
CW	Continuous Wave

DCM	Dilated Cardiomyopathy
ECG	Electrocardiography
EF	Ejection Fraction
EPI	Echo Planar Imaging
EROA	Effective Regurgitant Orifice Area
ESC	European Society of Cardiology
Ex-CMR	Exercise Cardiovascular Magnetic Resonance
ExPHT	Exercise induced Pulmonary Hypertension
FB	Free Breathing
FOV	Field of View
HF	Heart Failure
HR	Heart Rate
HR_{max}	Maximal Heart Rate
HRR	Heart Rate Reserve
i	Indexed to Body Surface Area
ICC	Intra-Class Correlation
IE	Infective Endocarditis
IHG	Isometric Handgrip
IQR	Inter Quartile Range
LA	Left Atrial
LGE	Late Gadolinium Enhancement
LV	Left Ventricle
LVCR	Left Ventricular Contractile Reserve
LVEDV	Left Ventricular End-Diastolic Volume
LVEDVi	Indexed Left Ventricular End-Diastolic Volume
LVEF	Left Ventricular Ejection Fraction
LVESD	Left Ventricular End-Systolic Dimension
LVESV	Left Ventricular End-Systolic Volume
LVESVi	Indexed Left Ventricular End-Systolic Volume
LVM	Left Ventricular Mass

LVMi	Indexed Left Ventricular Mass
LVOT	Left Ventricular Outflow Tract
LVSV	Left Ventricular Stroke Volume
LVSVi	Indexed Left Ventricular Stroke Volume
MI	Myocardial Infarction
MPS-SPECT	Myocardial Perfusion Scintigraphy by Single Photon Emission Computed Tomography
MR	Mitral Regurgitation
MR-CPET	Magnetic Resonance augmented Cardiopulmonary Exercise Test
MR-RF	Mitral Regurgitant Fraction
MR-Rvol	Mitral Regurgitant Volume
MRS	Magnetic Resonance Spectroscopy
MVr	Mitral Valve Repair
MVR	Mitral Valve Replacement
MVRar	Mitral Valve Replacement after Attempted Repair
NYHA	New York Heart Association
PAH	Pulmonary Arterial Hypertension
PCI	Percutaneous Coronary Intervention
PCMR	Phase Contrast Magnetic Resonance
PISA	Proximal Isovelocity Surface Area
PMVL	Posterior Mitral Valve Leaflet
PPVI	Percutaneous Pulmonary Valve Implantation
PR	Pulmonary Regurgitation
PW	Pulsed Wave
RA	Right Atrial
RAA	Right Atrial Area
RPE	Rate of Perceived Exertion
RV	Right Ventricle
RVEDVi	Indexed Right Ventricular End-Diastolic Volume
RVESVi	Indexed Right Ventricular End-systolic volume

RVOT	Right Ventricular Outflow Tract
RVSV	Right Ventricular Stroke Volume
RVSVi	Indexed Right Ventricular Stroke Volume
SCMR	Society of Cardiovascular Magnetic Resonance
SENSE	Sensitivity Encoding
SV	Stroke Volume
SVC	Superior Vena Cava
TAPSE	Tricuspid Annulus Plane Systolic Excursion
TAVI	Transcatheter Aortic Valve Implantation
TE	Echo Time
TFE	Turbo Field Echo
TGA	Transposition of the Great Arteries
THR	Target Heart Rate
TIA	Transient Ischaemic Attack
TMVI	Transcatheter Mitral Valve Implantation
TOE	Transoesophageal Echocardiography
TR	Repetition Time
TR-RF	Tricuspid Regurgitant Fraction
TTE	Transthoracic Echocardiography
VC	Vena Contracta
VENC	Velocity Encoding
VO2max	Maximal oxygen uptake
VTI	Velocity Time Integral

Chapter 1 Introduction

1.1 Mitral Regurgitation: aetiology, investigation and management

Mitral regurgitation (MR) is the second commonest valve lesion in Europe after aortic stenosis (1) and is defined as the retrograde flow of blood from the left ventricle into the left atrium (2). MR occurs due to the dysfunction of one (or more) anatomical components of the complex mitral apparatus. As such, anatomical understanding and appropriate imaging are required to diagnose the aetiology of mitral regurgitation to guide optimal management (3).

1.1.1 Mitral valve anatomy

The mitral valve anatomy consists of the mitral annulus, anterior and posterior valve leaflets which meet at the commissures and are attached to anterolateral and posteromedial papillary muscles respectively by chordae tendinae (4). MR can occur as the result of dysfunction in any of these anatomical components therefore an accurate description and thorough understanding of these components is important (3).

1.1.1.1 Mitral annulus

The mitral annulus is the anatomical junction between the endocardium of the left atrium, the valve proper and the left ventricular endocardium and myocardium (5). The mitral annulus is divided into anterior and posterior sections and serves as the insertion point for the 2 leaflets. The anterior annulus attaches to the fibrous trigone, however the posterior annulus is less supported with fibrous tissues, as

such the posterior annulus is prone to enlarge with left ventricular (LV) or left atrial (LA) dilatation (6). The mitral annulus forms a 3D saddle shape, during diastole the annulus moves with the posterior wall of the LV, creating a more circular shape for inflow. During systole, when the valve is closed, the annulus reverts back to an asymmetrical shape, with the long axis between the commissures and the short axis in the antero-posterior direction (5).

1.1.1.2 Leaflets

The mitral leaflet anatomy is illustrated in Figure 1-1 and has 2 leaflets; the anterior (AMVL) and posterior (PMVL) mitral valve leaflets. The AMVL has a semi-circular shape and attaches to 2/5 of the annular circumference and as per the Carpentier segmental leaflet classification, it is divided into 3 scallops: A1; anterior, A2, middle and A3 posterior (7). The PMVL is quadrangular in shape and attaches to 3/5 of the annular circumference and is divided into 3 scallops by 2 indentations: P1 the anteromedial scallop, P2 the middle scallop and P3 the posteromedial scallop (6). Unlike the PMVL that has indentations to demarcate the scallops, the AMVL does not, therefore scallops are defined by comparison to the opposing PMVL scallops. Identification of the differing scallops is important in describing pathology of the valve. In a normally functioning mitral valve the coaptation length of the leaflets is often several millimetres in length to ensure competency against high LV end-systolic pressures (4).

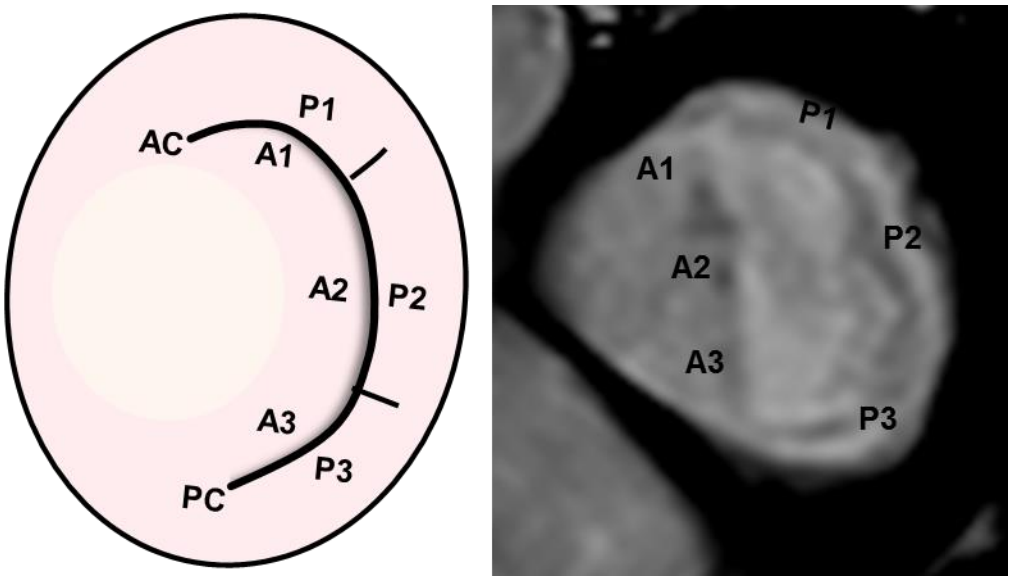


Figure 1-1 Anatomy of the mitral valve leaflets

An original illustration of a closed mitral valve (left) and short axis CMR image of an open mitral valve (right) depicting the mitral valve leaflets, anterolateral (AC) and posteromedial commissures (PC) and indentations in the posterior leaflet dividing it into the anteromedial scallop (P1), middle scallop (P2) and the posteromedial scallop (P3) thus allowing recognition of the opposing anterior (A1), middle A2 and posterior (A3) scallops of the anterior mitral valve leaflet.

1.1.1.3 Commissures

The commissures constitute the area where the AMVL and PMVL meet at the annular insertion point and are defined as the anterolateral commissure and posterolateral commissures. The commissures often overlap with millimetres of overlapping tissue between the leaflets (6).

1.1.1.4 Chordae tendinae

The chordae tendinae originate from the fibrous heads of the papillary muscles and are classified as either primary, if they insert into the free margins of the leaflets; secondary, if they insert into the body of the leaflets on the ventricular side or tertiary/basal if they connect the base of the PMVL and mitral annulus to the papillary muscle (4). The chordae tendinae control the positon of the leaflets at

end-systole with primary chordae preventing prolapse of the leaflet margins and secondary chordae preventing billowing (6).

1.1.1.5 Papillary muscles

Typically there are two papillary muscles which originate from between the apical and middle third of the LV free wall and provide chordae to both leaflets. The anterolateral papillary muscle consists of one body and head with a blood supply originating often from one or more left coronary branches. The posteromedial papillary muscle comprises two or more heads and more commonly receives blood supply from a single coronary artery (either the circumflex or right coronary artery depending on dominance) and is therefore more prone to injury in the event of myocardial infarction (8). As the papillary muscles attach in the LV, the LV can therefore directly affect MV anatomy. Changes in LV geometry can therefore result in poor coaptation of the MV by affecting papillary muscle position (6, 8).

1.1.2 Classification of MR

MR is commonly classified by the underlying aetiology and by using Carpentier functional classification. Classified by aetiology, MR is either primary/organic, a result of intrinsic disease of one or more valve components or can be secondary/functional, which is MR occurring as a result of alterations to LV or LA geometry (1). Carpentier's functional classification classifies MR by the effect the underlying lesion(s) has upon the motion of the free margin of the leaflet in relation to the annular plane (3, 9).

1.1.2.1 Carpentier's functional classification

Carpentier's functional classification is useful to guide optimal repair techniques (Figure 1-2). MR can occur in the context of normal leaflet motion (Type I) secondary to annular dilatation, clefts, perforations; due to excessive leaflet motion (Type II) as a result of chordal rupture or elongation; due to restricted leaflet

movement predominantly in diastole (Type IIIa) for example secondary to rheumatic disease; or restricted leaflet motion in systole (Type IIIb) which can be secondary to ischaemic or non-ischaemic regional or global LV remodelling with leaflet tethering (3, 9). The underlying lesions and possible aetiologies attributable to different Carpentier functional classifications are displayed in Table 1-1.

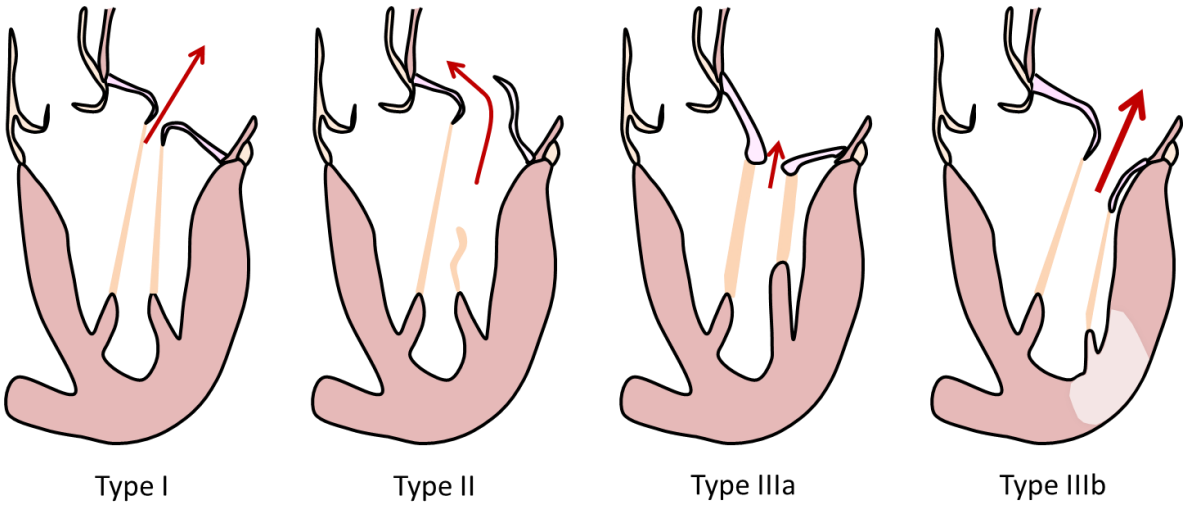


Figure 1-2 Original illustration depicting examples of Carpentier's functional classification.

Adapted from (3). Type I, normal leaflet motion; Type II, Increased leaflet motion; Type IIIa Restricted leaflet motion (diastole); Type IIIb Restricted leaflet motion (systole)

Table 1-1 Carpentier's functional classification of mitral regurgitation, corresponding lesions and possible aetiologies

Type	Leaflet	Lesion(s)	Aetiology
I	Normal Leaflet motion and length	Annular dilation	Dilated cardiomyopathy Atrial dilatation
		Leaflet perforation	Endocarditis
II	Excessive leaflet motion (leaflet prolapse)	Chordal elongation/rupture	Fibroelastic deficiency Barlow's disease Marfans/ Ehlos Danlos syndrome
		Papillary muscle elongation/rupture	Myocardial infarction Endocarditis Trauma
IIIa	Restricted leaflet motion (Diastole)	Leaflet calcification Leaflet thickening/retraction Commissural fusion Chordal thickening/fusion/retraction	Rheumatic heart disease Carcinoid heart disease Radiation Systemic Lupus Erythematosus Anti-phospholipid syndrome Cardiac amyloidosis
IIIb	Restricted leaflet motion (Systole)	Left ventricular dilatation Chordal tethering Papillary muscle displacement	Ischaemic cardiomyopathy Dilated cardiomyopathy

Adapted from (9, 10)

1.1.2.2 Classification by Aetiology: Primary MR

Primary/Organic MR results from intrinsic disease of the mitral valve apparatus. Degenerative mitral valve disease is the commonest form, other causes include: rheumatic disease, infective endocarditis, drug-induced and MR associated with systemic disease (11).

1.1.2.2.1 Degenerative MR

Degenerative mitral valve disease constitutes a spectrum of conditions in which structural lesions of the mitral valve are caused by connective tissue changes preventing normal functioning of the valve. There are two major phenotypes of degenerative disease that lead to mitral valve prolapse; Barlow's disease and fibroelastic deficiency (12).

Barlow's disease is the abnormal accumulation of mucopolysaccharides leading to mitral valve prolapse that occurs more commonly in younger (<60yrs), female patients. Pathologically there is myxoid infiltration which destroys the 3 layer leaflet architecture (myxomotous degeneration) and demonstrates collagen alterations on histological examination (12). Classically there is bi-leaflet thickening and redundancy (13), chordae are often thickened, fused or potentially calcified. The aetiology is unknown, however familial/genetic cases have been described (14). On echocardiography, Barlow's disease will often show billowing of the body of one or more leaflets and prolapse of the margin of one or more leaflets, with the latter allowing MR. MR often occurs in mid to late systole, if as a result of chordal elongation (12).

Fibroelastic deficiency is characterised by the loss of mechanical stability as the result of abnormalities in the connective tissue structure (15). There is a deficiency of fibroelastic tissue rather than an excess that occurs in Barlow's disease. As a result leaflets are thin and the chordae are thin and friable. MR often occurs as a result of rupture of the thin, deficient chords and therefore, commonly is the result of prolapse of a single scallop (16). Often patients present with a short duration of symptoms that have occurred after rupture of thinned chordae. Typically on

echocardiography a single prolapsing scallop is seen, most commonly P2. Billowing is not seen, annular dilatation is less significant than in Barlow's disease and annular calcification is rare. MR can occur throughout the entirety of systole, especially if as a result of chordal rupture (12).

Degenerative MR can also result from a syndrome of connective tissue disease. Marfans syndrome, Ehlos-Danlos syndrome, osteogenesis imperfecta and pseudoxanthoma elasticum often create a Barlow-type mitral valve disease. Marfans syndrome, like Barlow's, shows a high myxoid infiltration, but a tendency to more elastic fibre alterations (17).

1.1.2.2.2 Rheumatic MR

MR as a result of rheumatic heart disease is rare in the developed world, but still prevalent in developing counties (18). Mitral stenosis is more common in chronic rheumatic heart disease, however significant MR can also occur. In active/acute rheumatic heart disease, severe MR can occur as a result of annular dilatation, chordal elongation and anterior leaflet prolapse (19). Numerous studies demonstrate that rheumatic heart disease in young patients predominantly demonstrates isolated MR (often first decade of life), whilst mixed disease is more prominent in the second decade and isolated mitral stenosis occurs in later life (3rd decade onward) (20-22). It is therefore theorised that patients develop a varying degree of MR in the acute phase that remains and patients then develop mitral stenosis due to commissural fusion, leaflet thickening, and subvalvular disease. Similarly, it is theorised that pure mitral stenosis phenotypes of rheumatic heart disease potentially result from a milder carditis and thus minimal MR (23).

1.1.2.2.3 Infective endocarditis

Mitral valve infective endocarditis (IE) is the infection of a portion or the entirety of one or both mitral valve leaflets that can occur by a variety of pathogens including (but not limited to) bacterial, viral and fungal. Infective endocarditis is one of commonest causes of acute mitral regurgitation in the developed world (24). Mitral valve endocarditis can result in leaflet perforation, chordal rupture and even

complete leaflet destruction, therefore the resultant MR can vary in appearance and severity. Additional findings on echocardiography can include the presence of a vegetation, abscess or pseudoaneurysm and new dehiscence of a prosthetic valve, all of which are major criteria in the diagnosis of IE (25).

1.1.2.3 Classification by Aetiology: Secondary MR

In secondary MR the mitral valve is structurally normal, however its function is impaired as the result of either distorted LV geometry, most commonly by dilated or ischaemic cardiomyopathy, or as a result of annular dilatation caused by LA dilatation, most commonly in patients with chronic atrial fibrillation (AF) (1).

1.1.2.3.1 Ischaemic MR

The mitral valve is reliant on the papillary muscles for correct function (6). The anterolateral papillary muscle is supplied by the circumflex artery with secondary supply from the left anterior descending artery. The posteromedial papillary muscles coronary supply is variable, generally from the circumflex in a left dominant system and from the right coronary artery in a right dominant system (26). Ischaemia or infarction in the territory of the supplying arteries can therefore result in papillary muscle dysfunction and therefore MR of an otherwise structurally normal mitral valve. Often with a single coronary blood supply, the posteromedial papillary muscle is more susceptible to an ischaemic insult. In rare cases the papillary muscle can be directly affected by an infarct causing complete or partial papillary muscle rupture, often resulting in acute torrential MR (27). However, the majority of ischaemic MR cases are a result of papillary muscle dysfunction caused either by localised regional wall motion abnormalities adjacent to the papillary muscle or by papillary muscle displacement, which provokes increased tethering of the mitral valve leaflets (28). Ischaemic MR predominantly occurs post myocardial infarction (MI), one study demonstrating mild MR in 38% and moderate/severe MR in 12% within 30 days post infarction (29). It can occur as part of acute ischaemia creating intermittent ‘flash’ pulmonary oedema, however MR from intermittent single vessel occlusion is often mild without an underlying ventricular abnormality (30).

1.1.2.3.2 Functional MR

Functional MR is the result of an imbalance between leaflet tethering forces and decreased closing forces (31). Increased leaflet tethering is principally caused by adverse left ventricular remodelling resulting in apical shift of the papillary muscle thus causing leaflet tethering and abnormal coaptation (32). Leaflet remodelling, in terms of increased leaflet thickness and length, is a common response, however insufficient leaflet remodelling, relative to the mitral annular and LV changes, is independently associated with the severity of functional MR (33). Decreased mitral valve closing forces can cause functional MR and occur due to reduced LV contractility and/or synchronicity (31). Functional MR is common in dilated cardiomyopathy (DCM) and the severity of functional MR is strongly associated with outcomes of heart failure (HF) patients independent of LV function (34). Recently, the concept of proportionate and disproportionate functional MR in patients with chronic HF with reduced ejection fraction has been described. Proportionate functional MR is where there is a linear relationship between the LV end-diastolic volume (LVEDV) and effective orifice area of the mitral valve. These patients respond well to treatments that reverse LV remodelling such as neurohormonal agonists and LV assist devices. Disproportionate MR occurs when ventricular dyssynchrony causes unequal contraction of the papillary muscles and thus functional MR greater than expected for the patient's LVEDV. HF with reduced ejection fraction patients with disproportionate MR respond well to treatments of any underlying dyssynchrony (e.g. cardiac resynchronisation) and/or the mitral valve leaflets (e.g. transcather mitral valve repair) (35).

1.1.2.3.3 Atrial Functional MR

Atrial functional MR occurs as the result of isolated mitral annular dilatation and inadequate leaflet adaptation despite typically normal LV size and function. Atrial functional MR typically occurs in the context of AF and/or HF with preserved ejection fraction with severe LA dilatation (31).

1.1.3 Imaging Mitral Regurgitation

The comprehensive evaluation of any valve disease requires the accurate assessment of the valve morphology, severity of the specific valve lesion and assessment of the resultant effects on adjacent cardiac structures. For the assessment of MR, evaluation of valve anatomy, regurgitation severity, biventricular dimensions/function, left atrial size and any resultant pulmonary hypertension can help to guide optimal patient management (36). Transthoracic echocardiography (TTE) is the advised first line investigation for MR assessment (1, 37), with transoesophageal echocardiography (TOE) a common second line modality in borderline cases or where TTE image quality is poor. Cardiovascular magnetic resonance (CMR) has developed as a useful imaging modality to be used as an adjunct to echocardiography, especially in borderline cases or those with suboptimal echocardiographic windows (38).

1.1.3.1 Transthoracic Echocardiography

TTE is the recommended first line investigation in mitral regurgitation assessment, as a result of it being a widespread, cheap and portable modality (1, 39). The European Society of Cardiology (ESC) and American Heart Association (AHA) guidelines both advise that MR is assessed using an integrated approach. This involves a combined assessment using semi-quantitative, quantitative and qualitative measurements to determine MR severity and various views to assess morphology (1, 39, 40). These assessments are to define MR as mild, moderate or severe. Additionally, MR can be defined as mild (1+), moderate (2+), moderate-severe (3+) and severe (4+). Table 1-2 demonstrates the severity definitions assessed by various parameters as per the American Society of Echocardiography (ASE) guidelines (40). Below each assessment method will be described in-depth.

Table 1-2 Integrated echocardiographic severity grading criteria as per the American Society of Echocardiography

		Mitral regurgitation severity			
Approach	Parameter	Mild	Moderate		Severe
Structural	Mitral valve morphology	No or mild leaflet abnormality	Moderate leaflet abnormality or moderate tenting		Severe valve lesions (primary: flail leaflet, ruptured papillary muscle, severe retraction, large perforation; secondary: severe tenting, poor leaflet coaptation)
	LV/LA size	Usually normal	Normal or mildly dilated		Dilated
Qualitative	Colour flow jet area	Small, central, narrow, often	Variable		Large central jet (>50% of LA) or eccentric wall-impinging jet of variable size
	Flow convergence	Not visible, transient or small	Intermediate in size and duration		Large throughout systole
	CW Doppler jet	Faint/partial/parabolic	Dense but partial or parabolic		Holosystolic/dense/ Triangular
Semi-quantitative	VC width (cm)	<0.3	Intermediate		≥0.7 (>0.8 for biplane)
	Pulmonary vein flow	Systolic dominance (may be blunted in LV dysfunction or AF)	Normal or systolic blunting		Minimal to no systolic flow/ systolic flow reversal
	Mitral inflow	A-wave dominant	Variable		E-wave dominant (>1.2 m/sec)
Quantitative	EROA, 2D PISA (cm^2)	<0.20	0.20-0.29	0.30-0.39	≥0.40 (may be lower in secondary MR with elliptical ROA)
	Rvol (ml)	<30	30-44	45-59	≥60
	RF (%)	<30	30-39	40-49	≥50

Adapted from the ASE guidelines (40). Abbreviations: 2D-PISA, 2-dimensional proximal isovelocity surface area; AF, atrial fibrillation; CW, continuous-wave; EROA, effective regurgitant orifice area; LV, left ventricle; LA, left atria; MR, mitral regurgitation; RF, regurgitant fraction; RVol, regurgitant volume; VC, vena contracta

1.1.3.1.1 Qualitative assessment

Morphology assessment

TTE is the mainstay of assessing morphology of the mitral valve to assess underlying aetiology via a 2D approach (41). 3D-TTE can assist in identifying the location of valvular lesions, but the current lower spatial and temporal resolution of 3D-TTE is a limitation when assessing valvular structure (39). In the pre-operative setting, if valve morphology is unclear from TTE, then further assessment via TOE may be required (41).

Colour flow Doppler

Visual assessment of the colour flow Doppler jet can give pointers towards the severity of MR, but should rarely be used in isolation to define severity. The colour flow jet area can be used to exclude MR, but is poor at defining severity as it can vary significantly dependant on afterload conditions such as blood pressure (BP) and the regurgitant jet eccentricity (42). Via a visual qualitative assessment, central jets are prone to overestimation, due to blood pool entrainment in the LA, and eccentric jets to underestimation due to the Coanda effect, whereby eccentric jets impinge upon the LA wall and follow parallel to the line of the wall, thereby decreasing the visual impression of the jet severity (43). Therefore any jet other than a small central MR jet, should be further assessed semi-quantitatively via the flow convergence/ proximal isovelocity surface area (PISA) and vena contracta methods (38).

Continuous wave Doppler intensity

The density and contour of the MR continuous wave (CW) Doppler trace can be useful in determining MR severity with a holosystolic dense and triangular shaped CW Doppler trace consistent with severe MR and a faint or partial Doppler trace

more common with mild MR (40). However, the technique has several limitations. As with all Doppler measurements it is highly reliant upon the Doppler alignment with the jet. This can create inaccuracies, for example, a CW Doppler trace poorly aligned to an eccentric jet could appear incorrectly less severe. The descriptors for moderate MR rely upon the absence of either mild or severe descriptors rather than having specific criteria (38). Given the described limitations of qualitative methods of assessing MR by echocardiography quantitative and semi-quantitative methods have developed.

1.1.3.1.2 Semi-quantitative assessment

Vena contracta

The vena contracta (VC) is the narrowest portion of regurgitant flow that occurs directly downstream of the regurgitant orifice. The VC width is therefore used as a measure of the effective regurgitant orifice and has become an important TTE assessment for MR as it correlates well with quantitative Doppler techniques in both central and eccentric jets (44). Preferably, in MR, the VC should be measured in the parasternal long axis view. A VC width of <0.3cm denotes mild MR and ≥0.7cm severe MR. However, there is significant overlap of intermediate values, therefore the use of an additional assessment, such as PISA, is advised in such instances. Limitations with this method arise in the underestimation of MR severity when multiple jets are present and errors that can occur in jets arising from a non-circular orifice (40). Additionally, as the measurement being made is small with only ≥0.7cm measurement required for severe MR, then slight errors can result in severity misclassification (38).

Pulsed wave Doppler measures

Pulsed wave (PW) Doppler can provide additional semi-quantitative assessment (Table 1-2). For example, on mitral inflow assessment by PW Doppler, an E-wave velocity of ≥1.2m/s is suggestive of severe MR, whilst a dominant A-wave makes

severe MR very unlikely. Additionally, the presence of reverse systolic flow in the pulmonary veins, using PW Doppler, is supportive of severe MR (40)

1.1.3.1.3 Quantitative assessment

Several Doppler techniques exist to perform quantitative assessment of MR by echocardiography and derive the mitral regurgitant volume (MR-Rvol), regurgitant fraction (MR-RF) and effective regurgitant orifice area (EROA), which are parameters indicative of MR severity (40). MR-Rvol is the blood volume that regurgitates with each heart beat (ml/beat) and a measure of absolute volume overload. MR-RF is the percentage of the LV stroke volume (LVSV) that regurgitates back through the mitral valve with each beat. EROA is the mean area of the systolic regurgitant orifice (38). The echocardiographic Doppler techniques used to calculate these parameters are: the quantitative volumetric method, the pulsed Doppler method and the flow convergence (PISA) method (38).

Quantitative volumetric method

The quantitative volumetric method relies on the fact that blood is incompressible and the conversion of mass principle. Essentially, blood leaving the left ventricle that does not leave through the aorta, in the context of no intracardiac shunts, must leave back through the mitral valve (MR-Rvol). The aortic stroke volume (SV) and LVSV must be measured to quantitate MR by this method. The aortic SV is calculated as shown in Equation 1 from measurements of the LVOT diameter using 2D echo and LVOT velocity time integral (VTI) using PW Doppler. LVSV is calculated from LVEDV and LV end-systolic volume (LVESV), measured from 2D echocardiographic measurements. As per Equation 2, MR-Rvol is calculated by minusing aortic SV from LVSV, MR-RF calculated as the percentage of LVSV regurgitating back through the mitral valve and EROA calculated from dividing the MR-Rvol by the VTI of the MR jet. The pitfall of this technique can occur if LV volume is underestimated, often due to foreshortening or poor acoustic windows

(40). This can result in underestimating the MR severity, but can be improved with the use of contrast or 3D-echocardiography (45, 46).

Equation 1 – Calculating valve stroke volume with annular and PW Doppler measurements

$$Valve_{CSA} = 0.785\ x\ Valve\ annulus\ diameter^2$$

$$Valve\ SV = Valve_{CSA}\ x\ Valve_{VTI}$$

Equation 2 – Echocardiographic MR quantification (volumetric method)

$$LV_{SV} = LVEDV - LVESV$$

$$MR_{Rvol} = LV_{SV} - Aortic_{SV}$$

$$MR_{RF} = \frac{MR_{Rvol}}{LV_{SV}}\ x\ 100\%$$

$$EROA = \frac{MR_{Rvol}}{MR_{VTI}}$$

Pulsed Doppler method

Similar to the quantitative volumetric method the pulsed Doppler method also utilises the conversion of mass principle assessing the blood flow leaving the left ventricle, however, it utilises mitral inflow rather than LVSV, assuming that the volume of blood that enters the LV (mitral inflow/ mitral stroke volume) that doesn't leave via the aorta must, in the context of no intra-cardiac shunts, leak back through the mitral valve (MR-Rvol). The method uses PW Doppler measurements at the aortic and mitral annulus, as the annulus is deemed to have the least anatomical variability of the valve apparatus. Cross sectional areas (CSA) are calculated from measurements of the valve annular diameters and valve stroke volume measured from CSA and VTI measured by PW Doppler as shown in Equation 1. MR-Rvol, MR-RF and EROA can therefore be derived from the mitral and aortic stroke volumes and mitral regurgitation VTI as shown in

Equation 3 (40). A limitation of the technique can arise if inaccurate measurements of the valve annular diameters occur, as slight errors in measurement can lead to significant errors (38).

Equation 3 – Echocardiographic MR quantification (Pulsed Doppler method)

$$MR_{Rvol} = Mitral\ SV - Aortic\ SV$$

$$MR_{RF} = \frac{MR_{Rvol}}{Mitral_{SV}}\ x\ 100\%$$

$$EROA = \frac{MR_{Rvol}}{MR_{VTI}}$$

Flow convergence (PISA) method

Also known as the PISA method, the method assesses flow convergence that occurs proximal to the regurgitant orifice to quantitate MR, as flow through the convergence zone is assumed to be equivalent to flow through the regurgitant orifice (38). Flow convergence commonly forms hemispheric shells of decreasing area and increasing velocity (47) that can be visualised with colour flow Doppler. By reducing the Nyquist limit to 15-40cm/s and imaging in the apical 4-chamber view (or parasternal view for AMVL prolapse) a PISA radius can be measured (38). The PISA radius is measured from the VC to the colour Doppler aliasing threshold (seen as a demarcated colour change from yellow to blue, when jet direction is away from the transducer); this is used to calculate the area of the flow convergence hemisphere, which when multiplied by the aliasing velocity can be used to calculate the regurgitant flow (40). Regurgitant flow can then be used in combination with CW Doppler measurements of the regurgitant MR jet to calculate the EROA and MR-Rvol (38). The calculations required to perform the flow convergence/PISA MR quantification method are shown in Equation 4.

Equation 4 – Echocardiographic MR Quantification (flow convergence method)

$$Regurgitant\ flow = 2\pi r^2\ x\ Nyquist\ velocity$$

$$EROA = \frac{Regurgitant\ flow}{MR_{peak\ velocity}}$$

$$MR_{Rvol} = EROA\ x\ MR_{VTI}$$

The flow convergence/PISA method makes several geometric assumptions which can result in errors in MR quantification if not true and therefore has some limitations. The method assumes a hemispheric flow convergence into a circular orifice that occurs at a planar angle. However, this is not always the case, especially in secondary MR where the regurgitant orifice can be elongated by LV dilatation and therefore be crescent shaped, in which the method can result in underestimation of quantitated MR (40). Additionally, given the PISA measurement calculates an instant peak flow rate it may not equal the average orifice area throughout the entirety of the regurgitation. To best represent an average EROA the PISA measurement should be performed at the time of peak regurgitant velocity. However, as MR jets can be dynamic, the method can result in underestimation in bimodal regurgitant flow, such as can occur in secondary MR or overestimation with late-systolic regurgitant flow, which can occur in primary MR (40).

1.1.3.2 Transoesophageal Echocardiography (TOE)

TOE has many benefits for assessing MR and is useful when TTE has been technically difficult or inconclusive, for planning MV surgery or percutaneous procedures and for intra-operative use. In general TOE is more accurate at defining MV pathology (40) and therefore useful pre-operatively to determine the likelihood of a successful repair. This is an important assessment given the variable outcomes that the underlying aetiology has on the durability/success of MV repair (48) and can be a determinant factor in advising early surgical

intervention as per international guidelines (1, 39). TOE uses many of the same methods to quantify MR as TTE, but the superior image quality likely makes measurements more accurate (40). However, due to its invasive nature, it is not ideal for sequential assessment (41) and given sedation is often required or general anaesthetic during intra-operative TOE; this can lower blood pressure, therefore reducing afterload, which can reduce MR severity (49).

1.1.3.3 Cardiovascular Magnetic Resonance

CMR is able to measure MR severity and the resultant effect on biventricular volumetrics and function accurately. Using balanced steady state free precision (bSSFP) sequences, blood pool has natural contrast to myocardium without need for intravenous contrast (50) and CMR allows imaging in any plane, without restriction due to body habitus and does not use ionizing radiation. As such, CMR has become the reference standard assessment for biventricular volume assessment (51, 52). Additionally, CMR is useful to assess mitral valve morphology in cases where echocardiography has been suboptimal (41). In addition to standard 2 and 4-chamber cine imaging, sequences can be planned to transect the mitral valve at the coaptation line of individual scallops to accurately identify the site of pathology (53). However, the lower spatial and temporal resolution of CMR, compared with echocardiography, can result in suboptimal assessment of subvalvular apparatus (e.g. ruptured chordae/flail leaflet) or vegetations (54).

CMR can be used to perform qualitative (visual), semi-quantitative and quantitative assessment of MR severity. Qualitative assessment involves visualising the MR regurgitant jet in the left atrium on cine imaging, which is often visible due to the high velocity jet causing signal loss/spin dephasing (55). However, caution must be used with visual assessment as jet appearance can be significantly impacted by CMR parameters such as sequences used and echo time (56), therefore quantitative methods are preferred. Carefully planned cine imaging allows planimetry of the anatomical regurgitant orifice area, but it can be difficult to accurately align imaging planes and can resultantly be time consuming (38, 57).

CMR benefits from accurate quantification of MR, which can be done via indirect or direct methods, which shall be presented including their pros/cons.

1.1.3.3.1 Direct MR quantification by CMR

Direct MR quantification by CMR, involves CMR imaging of the MR jet using Phase contrast magnetic resonance (PCMR) sequences planned in line to the MR jet to quantitate regurgitant volume. Maximal velocity encoding must be set high to avoid aliasing. The use of only one measurement (rather than a combination of two with indirect MR quantification methods) is an advantage of the method. However as the PCMR imaging must be planned in line to the MR jet, eccentric jets or multiple jets can result in inaccuracies by this method and dynamic motion of the mitral annulus during ventricular systole can make the PCMR sequences technically difficult to plan and apply (58).

1.1.3.3.2 Indirect MR quantification by CMR

Indirect MR quantification involves the combination of two separate measurements to quantitate MR. The main methods of indirect MR quantification by CMR are:

1. Using LV and aortic stroke volumes (LVSV-AoSV method)
2. Ventricular stroke volume comparison (LVSV-RVSV method)
3. Using mitral inflow and aortic forward flow (Mitral annular method)

LV and aortic stroke volume method (LVSV-AoSV method)

The LVSV-AoSV method works via the conversion of mass principle and assumes that no intra-cardiac shunts are present involving the left ventricle. The method assumes that blood pumped by the left ventricle, that doesn’t leave through the aorta, must leak back through the mitral valve (MR-Rvol). LVSV are derived from short axis cine imaging as the calculation of LVEDV-LVESV. Aortic SV are acquired from aortic PCMR imaging. MR-Rvol is calculated as LVSV-aortic SV (Equation 5). An example of the calculation is presented in Figure 1-3.

Equation 5 – CMR indirect MR quanfication (LVSV-AoSV method)

$$MR_{Rvol} = LV_{SV} - Aortic_{SV}$$

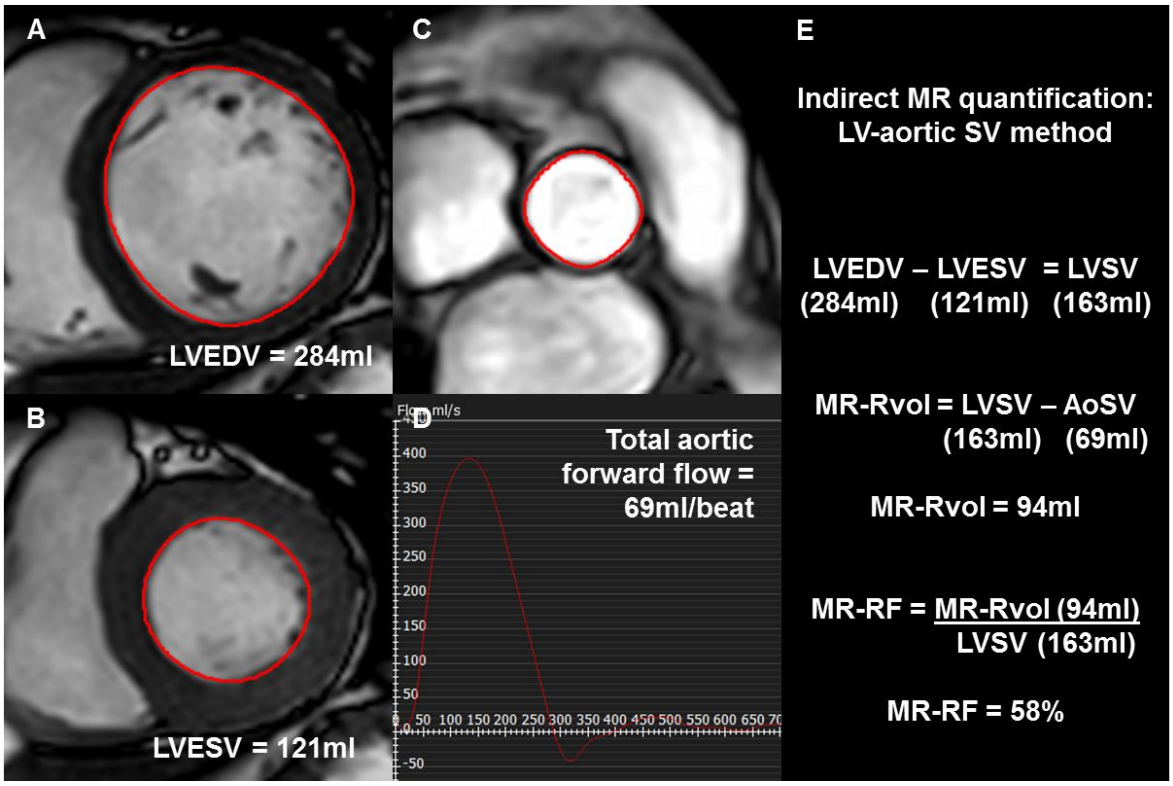


Figure 1-3 CMR MR quantification by the LV-Aortic stroke volume method

Short axis cine stack is contoured from base to apex at end-diastole (A) and end-systole (B) to provide left ventricular end-diastolic and end-systolic volumes respectively. The ascending aorta is contoured in every phase on the aortic phase contrast magnetic resonance flow imaging (C) to provide the aortic flow loop (D) and total aortic forward flow volume. MR regurgitant volume and fraction are calculated from the provided measurements (E).

The LVSV-AoSV indirect CMR method of MR quantification is often preferred due to numerous advantages. The method does not rely on geometric assumptions, unlike echocardiographic methods (38, 59, 60), and is not adversely affected by the number or eccentricity of the MR jet or the presence of aortic, pulmonary or tricuspid regurgitation unlike some CMR quantification methods (58). The method has demonstrated superior diagnostic accuracy over the CMR mitral annular method in detecting significant MR in mitral valve prolapse (61). Additionally the method has demonstrated superiority over TTE with superior reproducibility (59, 60, 62, 63) and prognostic assessment of MR (63, 64). However, the method relies on accurate LV volume analysis, for which there are two accepted contouring methods which differ on whether LV trabeculation and papillary muscles are included as part of the blood pool or not. Including LV trabeculation and papillary muscles as part of the blood pool results in better reproducibility but results in higher LVSV and thus higher quantitated MR-Rvol, this must be taken into account when interpreting results and performing subsequent CMR to ensure the same method is used (58).

Ventricular stroke volume comparison method (LVSV-RVSV method)

In the context of no intracardiac shunts or valve disease the stroke volumes from the left and right ventricle should be equivalent. Therefore using the conversion of mass principle and in the context of no intracardiac shunts or other valve disease then LVSV and right ventricular stroke volume (RVSV) can be used to calculate MR-Rvol by Equation 6 (58).

Equation 6 – CMR indirect MR quantification by ventricular stroke volume method (LVSV-RVSV method)

$$MR_{Rvol} = LV_{SV} - RV_{SV}$$

The advantage of the ventricular stroke volume method is it can be calculated from short axis cine imaging without the need for PCMR sequences and therefore the

acquisition is time efficient. However, significant disadvantages make it less utilised and robust than the LVSV-AoSV method. The method is inaccurate in the context of intra-cardiac shunts or other valve disease. The significant prevalence of tricuspid regurgitation in the MR population can therefore limit its application (65, 66). Additionally, as described above in presentation of the LVSV-AoSV method, the same caveats regarding methods of LVSV calculation apply; indeed, the issue is escalated in additionally requiring accurate contouring of right ventricular (RV) volumes, which often demonstrate greater variability than LV volumes (58).

Mitral inflow and aortic outflow method (Mitral annular method)

Also known as the mitral annular flow method, PCMR sequences are used to calculate mitral inflow and aortic stroke volume to derive MR-Rvol, as shown in Equation 7. Mitral inflow is assessed with PCMR imaging planned at the midpoint of the mitral leaflets whilst open in diastole. The mitral inflow (diastolic component) is measured and the mitral regurgitation (systolic component) is ignored (58). Aortic stroke volume is derived from PCMR imaging as previously described.

Equation 7 CMR indirect MR quantification (mitral annular method)

$$MR_{Rvol} = Mitral\ inflow - Aortic_{SV}$$

The mitral annular method suffers from a similar issue as the direct method of MR quantification by CMR, as regards difficulties that can arise in accurately planning and performing PCMR imaging on a mitral annulus that is often highly mobile throughout the cardiac cycle (58).

Optimal CMR quantification method

As described, the direct and indirect CMR methods to quantify MR have varying pros and cons. Studies comparing reproducibility between methods provide conflicting results. The LVSV-AoSV method has demonstrated superior intra/inter-observer reproducibility to the LVSV-RVSV method in several studies (60, 67) and over the mitral annular method in a study by Le Goffic *et al* (61). Conversely, Polte *et al* studied reproducibility of all indirect methods finding that the mitral annular method had superior inter-observer reproducibility, followed by the LVSV-AoSV method with the LVSV-RVSV method the worst with Coefficient of Variance (CV) of 10%, 14% and 18% respectively. Intra-observer variability was similar between the LVSV-AoSV and mitral annular methods, but worse with the LVSV-RVSV method with CV of 5%, 5% and 7% respectively. The results were driven by greater inter-observer variability on contouring the ventricles than PCMR flow imaging (68). Therefore no technique has emerged as clearly the most reproducible (58). However, more studies demonstrate the LVSV-AoSV method as the most reproducible (60, 61, 67) and it has been used in multiple studies to show superior reproducibility (59, 60, 62, 63) and prognostication compared to TTE (63, 64) and as such is the recommended MR quantification technique by the Society of Cardiovascular Magnetic Resonance (SCMR) (69).

1.1.3.3.3 CMR vs echocardiography in the assessment of MR

Several studies have compared CMR and echocardiographic assessment of MR severity, with the majority demonstrating moderate agreement between the modalities (59, 62, 63, 70, 71). The majority of comparative studies demonstrate superior reproducibility of MR quantification by CMR assessment (59, 60, 62, 63). In numerous studies, TTE overestimates MR severity compared to CMR (59, 63, 64, 71-73), of which several studies demonstrate superior prognostic assessment with CMR, suggesting it is more accurate (63, 64).

Myerson *et al* performed baseline CMR in 109 asymptomatic patients with moderate or severe primary MR on TTE and observed for up to 8 years (mean, 2.5±1.9 years) for symptom development or other indications for surgery. TTE

assessment was performed by integrated qualitative and quantitative assessment including assessment of EROA by the PISA method when feasible. CMR quantification of MR was by the LVSV-AoSV method. The study suggested a cut-off of MR-Rvol of >55ml or MR-RF of >40% as predicting those that progressed to symptoms or other indications for surgery within 5 years. 91% of patients remained free from surgery with an MR-Rvol ≤ 55ml reducing to 21% in those with MR-Rvol > 55ml (sensitivity 72%, specificity 87%). At 5 years patients with a MR-RF of ≤40%, 41-50% and >50% demonstrated surgical free survival in 89%, 59% and 16% respectively. In comparison, TTE EROA was less discriminatory; an EROA <0.4 cm^2 predicted surgery free survival in 86% decreasing to 64% with EROA ≥ 0.40cm^2 (64).

Penicka *et al* performed baseline CMR in 258 asymptomatic patients with at least moderate primary MR and preserved left ventricular ejection fraction (LVEF) (>60%) on TTE. Patients underwent combined TTE and TOE assessment with a CMR performed within 24hours. MR was assessed by TTE and TOE using an integrative approach and MR-Rvol was determined by an average value from PISA derived and Doppler volumetric methods. MR was quantified by CMR using the LVSV-AoSV method with aortic PCMR acquisition 2-3cm above the aortic valve. Severity of MR was classified as moderate or severe using ASE definitions (Table 1-2). Mean CMR derived MR-Rvol was 17ml smaller than echocardiography derived. 76% of grading into either moderate or severe MR was concordant between CMR and echocardiography. In the discordant cases, the majority occurred in patients with multiple or late systolic jets, which showed poor concordance with CMR derived MR-Rvol (Κ=0.2), whilst patients with holosystolic central jets showed very good concordance (Κ=0.9) which decreased to moderate concordance in those with eccentric jets (Κ=0.53). CMR derived MR-Rvol demonstrated the best area under the curve (AUC) in determining mortality (0.72) and in combination with need for mitral surgery (0.83). The study suggested a CMR quantitated MR-Rvol cut off of ≥50ml best able to predict adverse outcomes (all-cause mortality or progression to mitral surgery) during a median follow up of 5-years (63).

LV remodelling post-surgery for primary MR correlates more strongly with MR quantitated by CMR rather than TTE. Uretsky *et al* prospectively observed 103 patients with primary MR on TTE and performed baseline CMR. 38 patients subsequently underwent mitral surgery of which 26 had repeat CMR after 5-7 months. MR was assessed by integrative approach as per ASE guidelines with MR quantitated by the PISA method. MR was quantitated by CMR using the LVSV-AoSV method. MR severity correlation between CMR and TTE was modest overall (r=0.6), but poor in the cohort sent for surgery (r=0.4). Post-surgical LV remodelling correlated strongly with MR severity assessed by CMR (r=0.85), however there was no correlation between LV remodelling and echo defined MR severity (r=0.32). Significantly, only 32% of patients referred for surgery with severe MR, based upon echocardiographic assessment, had severe MR on CMR assessment (59). This finding was replicated in a recently published study in which 63 patients underwent CMR pre and post mitral valve 'correction'. LV reverse remodelling (change in LVEDV) correlated with baseline MR-Rvol (r=0.78) when assessed by CMR, however only 37% of patients had severe MR on CMR assessment, despite significant MR on TTE; indeed 13 patients (21%) had only mild MR on CMR. This led the authors to advise that CMR assessment of MR severity should be strongly considered in all patients prior to mitral valve correction/surgery (72).

Therefore, current studies comparing CMR vs echocardiographic assessment of MR suggest CMR MR quantification is more accurate (59, 72), more reproducible (59, 60, 62, 63), has superior prognostic value (63, 64) and that TTE may overestimate MR severity (59, 72). However, a few caveats exist with direct comparisons between TTE and CMR. CMR MR quantification using PCMR can be prone to background flow offset errors, which can make flow measurements inaccurate (74). This can be reduced by scanning the region of interest at the iso-centre of the MRI scanner, as this minimizes inhomogeneities in the magnetic field (75). Studies solely utilising the PISA method to quantitate MR by TTE may do TTE a disservice, as although it is the most utilised method (1), it has significant disadvantages in the context of eccentric jets, multiple jets or jets with a non-circular flow (76, 77). However, as demonstrated by Penicka *et al*, even when using combined TTE/TOE assessment and averaging two separate

echocardiographic MR quantification methods, CMR demonstrated superior prognostic ability (63). Additionally, current CMR vs echocardiography comparative prognostic studies did not utilise 3D-TTE, which has shown superior accuracy of MR quantification to 2D-TTE (76). Therefore, studies assessing prognostic outcomes of 3D-TTE vs CMR defined MR severity are warranted, but current evidence places CMR MR quantification as the reference standard.

1.1.3.3.4 CMR grading of MR severity

The severity grading thresholds of MR by CMR assessment are less clearly defined than echocardiography, with differing recommendations from individual research studies and international guidelines. Gelfand *et al* advises the severity grading as demonstrated in

Table 1-3, based upon a CMR study performed in 83 patients with MR, in which MR was quantified by the LVSV-AoSV method and thresholds developed to optimise correlation with severity on TTE (70). In 2017, the American Society of Echocardiography (ASE) and Society of Cardiovascular Magnetic Resonance (SCMR) collaboratively advised that due to the paucity of data, CMR should use the same severity thresholds of MR-Rvol/MR-RF as echocardiography as previously shown in Table 1-2 (40). However as described in chapter 1.1.3.3.3, TTE can overestimate MR compared with CMR and data from observational studies suggest lower CMR quantified MR thresholds in predicting adverse outcomes, with Myerson *et al* suggesting an MR-Rvol of 55ml and Penicka *et al* suggesting 50ml as a threshold of prognostic significance (63, 64). Therefore it is likely that CMR MR severity thresholds are lower than TTE. Larger studies spanning the range of MR severity guided by prognostic outcomes are required to better define CMR MR severity thresholds. However, a recently published consensus statement from international experts advises altered severity cut offs (

Table 1-4), based upon all available up to date evidence from comparative echocardiography and CMR studies with prognostic data (75).

Table 1-3 CMR defined MR severities as per Gelfand *et al*

MR Severity		Regurgitant fraction
1+	Mild	≤ 15%
2+	Moderate	16 – 25%
3+	Moderate-severe	26 – 48%
4+	Severe	>48%

Adapted from (70)

Table 1-4 Advised CMR MR severities grading from international consensus

Type of MR	Severity Grading			
	Mild	Moderate	Severe	Very severe
Primary	MR-RF <20%	MR-RF= 20-39%	MR-RF 40-50% MR-Rvol >55-60ml	MR-RF >50%
Secondary	MR-Rvol <30ml	MR-Rvol <30-60ml	MR-Rvol >60ml	N/A

Adapted from (75). Abbreviations: MR, Mitral regurgitation, Rvol, regurgitant volume, RF, Regurgitant fraction

1.1.3.4 Exercise imaging in MR

The timing of intervention in primary severe MR is guided by the presence of symptoms or adverse imaging biomarkers in asymptomatic patients (1, 39). However, symptoms are subjective and onset in chronic valve disease can be indolent, with patients often unaware of subtle changes in exercise tolerance (78). MR patients most often initially develop exertional symptoms prior to the disease deteriorating and developing resting symptoms. As MR patients naturally have a varied range of physical fitness with varied regular exertion levels, the timing of symptom development can differ between patients. Therefore, exercise imaging can be useful to objectively assess a patient's symptom status, individual functional capacity and determine imaging biomarkers that may benefit from early surgical intervention (1, 39, 78). As such, exercise imaging is typically used in 2 situations in MR: symptomatic patients with non-severe MR on resting imaging to assess if exercise regrades severity and in asymptomatic severe MR patients to detect symptoms. (79). Unfortunately dobutamine, which is commonly used in stress echocardiography, has afterload-reducing properties which can reduce the degree of MR, therefore its use is advised against in the assessment of primary MR (79, 80). Indeed, dobutamine stress and physical stress can result in differing haemodynamic responses in cardiac disease (81). Additionally, compared with exercise, pharmacological stress does not as accurately replicate the neurohormonal response, assess a patient's symptoms or functional state and can have more adverse events (80, 82). As such exercise imaging is the preferred first line stress assessment for MR (79, 83, 84). The following subchapters will discuss exercise imaging of MR including the currently identified imaging biomarkers that can assist in decision making in MR patients.

1.1.3.4.1 Exercise Echocardiography

Exercise echocardiography can provide additional prognostic information to resting TTE, with the absence of LV contractile reserve (LVCR) (<4% increase in LVEF or <2% increase in global longitudinal strain during exercise echocardiography) (85, 86), limited RV contractile recruitment (87), increase in MR severity (≥1 grade)(88)

or dynamic pulmonary hypertension (defined as an exercise rise in systolic pulmonary artery pressure (SPAP) to ≥60mmHg) (89, 90) during exercise echocardiography being predictors of poor prognosis.

Patients with poor LVCR more commonly develop LV dysfunction on observational follow-up (86) with worse post-operative LV function than those with preserved LVCR (85). Initial work by Leung *et al* demonstrated that latent LV dysfunction in MR patients could be indicated by a poor LVCR, demonstrated by an increase in LVEF of less than 4% on exercise echocardiography and this was associated with worse LVEF post-operatively (91). Subsequent work by Lee *et al* performed exercise echocardiography in 71 patients with isolated degenerative MR. During a mean follow up of 3±1years, 85% patients without LVCR progressed to mitral surgery compared with 42% with LVCR. The absence of LCVR was an independent predictor of poorer follow up LVEF and persistent post-operative LV dysfunction (85). More recent work by Magne *et al* suggested that LVCR was better assessed by changes in myocardial longitudinal function by assessing global longitudinal strain rather than changes in LVEF, demonstrating the absence of LVCR was independently associated with a 2-fold increase risk in cardiac events (86).

As regards exercise RV function, Kusunose *et al* investigated 196 patients with isolated moderate-severe MR, demonstrating that exercise tricuspid annular plane systolic excursion <19mm (TAPSE) was associated with valve-surgery free survival independent of resting LV/RV strain and exercise SPAP, suggesting that exercise RV dysfunction provides important incremental prognostic value in managing asymptomatic MR (87).

MR severity can change during exercise, as demonstrated in exercise echocardiography. Magne *et al* performed exercise echocardiography in 61 asymptomatic patients with moderate/severe degenerative MR to quantify changes in MR using the PISA method. 32% of patients had a marked increase in EROA (≥10mm^2) and MR-Rvol (>15ml). Patients with a rise in MR-Rvol >15ml had a worse symptom free survival than those with no significant rise or a decrease in MR-Rvol (88). However, in the ‘real-world’ setting, MR quantification during

exercise echocardiography can be difficult and not achievable in all patients. Coisne *et al* investigated 71 unselected patients with at least moderate MR (primary & secondary MR) and minimal or no symptoms. They found that quantitating EROA via the PISA method was feasible in 76% at rest in the supine position required for cycling; this decreased to 55% at peak exercise and was lower in patients with mitral valve prolapse at 43%. This was in contrast to the ability to assess LVCR and SPAP at peak exercise in 71% and 83% of patients respectively, therefore suggesting LVCR and SPAP assessment may be more reliable in the real-world setting (92).

Exercise induced pulmonary hypertension (ExPHT), identified on exercise echocardiography as developing exercise SPAP ≥60mmHg is associated with poorer observational and post-operative outcomes. Suzuki *et al* performed stress echocardiography on 49 patients with at least moderate MR on resting TTE, demonstrating worse 2-year symptom free survival in those with ExPHT (90). Additionally, Magne *et al* demonstrated worse post-operative outcomes in patients with ExPHT in a study involving 102 patients with primary MR and no/mild symptoms. All patients had baseline exercise echocardiography and underwent mitral valve surgery; those with ExPHT had significantly more cardiac events (postoperative cardiovascular-related death or cardiovascular-related hospitalisation, stroke or AF) than those without ExPHT at 39% vs 12% respectively.

As a result of such studies, international guidelines advise that exercise echocardiography is useful to risk stratify MR patients and also for patients where there is a discrepancy between MR severity and symptoms at rest (1, 37).

1.1.3.4.1 Exercise-CMR

Exercise cardiovascular magnetic resonance (Ex-CMR) has developed over the past three decades to combine the superior image quality of CMR with the first line advised method of stress by physical exercise. Ex-CMR as a modality is discussed in depth in Chapter 1.2. Given CMRs highly reproducible MR quantification and reference standard biventricular assessment, the possibility to assess bi-ventricular

function and quantitate MR during Ex-CMR is appealing. Only one Ex-CMR study has been performed in patients with MR by Chew *et al*, who demonstrated the feasibility of assessing biventricular volume assessment in 5 severe degenerative MR patients. However, MR quantification during exercise was not performed (93). Therefore further research is needed to develop a CMR protocol feasible to assess biventricular function and quantitate MR during Ex-CMR to take full advantage of the capabilities of CMR in this patient cohort.

1.1.3.5 Comparing imaging modalities in MR assessment

Multiple imaging modalities can be utilised to assess MR patients, each with intrinsic benefits and weakness, these are summarised in Table 1-5.

TTE is the advised first line investigation in MR assessment (1, 39). This is a result of significant benefits including widespread availability and cheap cost, portability and the ability to instantly visualise MR at the time of imaging. Both TTE/TOE share significant weaknesses including requiring the use of geometric assumptions in the assessment of MR, inaccuracies in the presence of eccentric or multiple jets and Doppler alignment issues that can reduce the accuracy of MR assessment (38). As a result an integrated assessment using qualitative, semi-quantitative and quantitative measures are advised as one single measurement is not sufficiently robust in the assessment of MR (40). TOE overcomes the limitation of acoustic windows that can reduce the accuracy of TTE assessments, but does not always guarantee good image quality. However, TOE generally offers the most accurate assessment of valve morphology of all imaging modalities and pathology localisation can be improved with the simultaneous use of real-time 3D-echocardiography (16). The invasive nature of TOE results in it not being ideal for serial assessment (41) therefore often reserved for borderline cases or pre/intraoperative use. CMR has the benefit of allowing imaging of the valve in any plane, but the decreased temporal resolution compared to echo can limit its use in morphological assessment (54). The main strength of CMR is the accurate quantification of MR, which appears to offer superior reproducibility (59, 60, 62, 63) and prognostic information to TTE (63, 64). This paired with it being the reference

standard for biventricular assessment (51, 52) results in it being a useful imaging modality for assessing MR. However, CMR is not widely available, is comparatively expensive, contraindicated in those with non-compliant implants, poorly tolerate by claustrophobic patients, does not allow an accurate instant assessment of MR severity at the time of imaging due to significant caveats with visual assessment and as discussed does not currently have universally accepted modality specific severity definitions (38). Dobutamine stress echocardiography, although in widespread use in CAD assessment, is advised against in MR assessment due its positive inotropic effect reducing MR severity (79). As such exercise echocardiography is preferred as a stress modality in MR. Assessment of changes in biventricular function, MR and PASP during exercise TTE provides additional prognostic information (85-90), but the modality suffers from the same weaknesses described above in resting TTE (38). In addition the majority of exercise-TTE relies on post stress imaging and therefore resulting in deceases in peak HR during imaging. In contrast Ex-CMR allows assessment of biventricular function during continuous exercise (93). However, further research is needed to allow quantification of MR during Ex-CMR and Ex-CMR as a modality is mostly a research tool, with minimal research performed in valve disease and therefore requires significant development before being clinically viable.

Table 1-5 Strengths/weakness of imaging modalities in MR assessment

Imaging modality	Strengths	Weaknesses
Transthoracic Echocardiography	Widespread availability Low cost Non-invasive Instant visualisation of MR	Acoustic windows Geometric assumptions Suboptimal Reproducibility Requires integrated assessment Doppler alignment issues Assessment of eccentric/multiple jets.
Transoesophageal Echocardiography	Instant visualisation of MR Fewer restrictions from acoustic windows Reference standard assessment of valve anatomy/morphology Intraoperative assessment	Invasive Geometric assumptions Suboptimal Reproducibility Requires integrated assessment Doppler alignment issues Assessment of eccentric/multiple jets.
Cardiovascular Magnetic Resonance	Image in any plane Excellent image quality Accurate & reproducible MR quantification Assessment of LV viability/scar Reference standard Biventricular volumes/function	Expensive & not widely available Claustrophobia Contraindications: non-compliant implants Lower temporal resolution than echo Limited evidence basis for defined severity cut offs
Exercise Echocardiography*	Additional prognostic information from assessment of LV/RV function, MR and PASP changes with exercise Allows assessment of haemodynamic & functional response to exercise Allows accurate assessment of exertional symptoms	Not all patients can tolerate exercise Often reliant on post stress imaging
Dobutamine Stress Echocardiography*	Technically easier to use than exercise echocardiography Feasible in patients unable to exercise	Inotropic effects of Dobutamine can reduce afterload and thus MR and is therefore advised against in MR assessment
Exercise Cardiovascular Magnetic Resonance**	Potential to utilise benefits of CMR during exercise Imaging feasible during continuous exercise	Research tool - not in clinical use in valve patients Minimal research in MR patients Not all patients can tolerate exercise

* In addition to the strengths/weakness of transthoracic echocardiography listed above. ** In addition to the strengths/weaknesses of CMR listed above.

1.1.4 Management of Primary MR

Primary MR is often a progressive disease. MR causes left ventricular and atrial enlargement, which in turn causes increase stress and damage to the mitral apparatus, such as annular dilatation which leads to increased EROA, coining the phrase ‘MR begets MR’ (39). As a result, MR-Rvol can progress from 5-7ml/year in primary MR (94). Severe primary MR patients have an excess mortality rate of 6.3% per year (11). There are no known medical treatments that alter the natural progression of severe primary MR, symptomatic patients may gain relief of symptoms by diuretics and afterload reduction but ultimately the only current treatment is surgical or percutaneous intervention (11).

The 2017 ESC guidelines (1) and the 2017 American Heart Association/American College of Cardiology (AHA/ACC) guidelines (39) provide similar guidance, as regards advising surgical intervention, with a few notable differences. Both guidelines advise mitral valve repair (MVr) as a Class I indication, when feasible above mitral valve replacement (MVR), if a successful and durable repair can be accomplished. Both advise surgical intervention as a Class I indication in symptomatic severe primary MR with LVEF>30%. However, for symptomatic primary MR patients with LVEF<30%, the AHA/ACC advise surgery as class IIb indication and the ESC advise medical therapy in the first instance. As per ESC guidance, if symptoms are refractory to medical treatment and the patient has low comorbidity then surgery is advised with repair if high likelihood of successful repair (class IIa) or replacement if not (class IIb). In the event surgery is deemed too high risk then extended medical therapy/percutaneous end-end repair is advised (class IIb) (1).

In asymptomatic patients, the guidelines differ slightly. Both guidelines advise surgical intervention as Class I indication where there is evidence of LV systolic dysfunction (LVEF<60%) or LV dilatation, defined as LV end-systolic dimension (LVESD) ≥45mm (ESC 2017 guidelines) or ≥40mm (AHA/ACC guidelines). The AHA/ACC do not extend this guidance to those with LVEF<30%. In asymptomatic patients with preserved LV size/function the ESC 2017 guidelines advise surgery

should be offered if there is new AF, PASP >50mmHg or there is a high chance of a durable repair with low surgical risk and the patient has LVESD>40mm and 1 of the following: flail leaflet or LA volume ≥60ml/m^2 in sinus rhythm (class IIa) (1). The AHA/ACC guidelines broadly provide the same guidance in asymptomatic patients with preserved LV size/function but are more liberal also advising surgery is reasonable if there is a progressive decline in LVEF or increase in LVESD (class IIa) (39).

1.1.4.1 MV repair

Mitral annuloplasty for primary MR was initially developed in the 1960s, however original techniques corrected insufficiency by narrowing the annulus. This resulted in 3 issues: 1, the correction resulted in altered anatomy of the valve leading to a degree of stenosis; 2, the localized plications used, focused tensile strength in a few critical points on the annulus, leading to a risk of sutures tearing out and 3, the original annuloplasty was still at risk of recurrent annular dilatation and therefore recurrent MR. Carpentier *et al* developed a surgical annuloplasty technique with the use of an annuloplasty frame/ring to overcome the described issues (95). Since this important development, MVr has progressed to become the recommended surgical technique to treat primary mitral regurgitation, when durable repair is likely (1, 39). Numerous surgical techniques have been developed, centring on the aims to restore/preserve correct leaflet mobility, to ensure appropriate leaflet coaptation and remodel and stabilise the annulus (96). Currently, successful repair is deemed likely, if performed by an experienced surgeon, in the vast majority of primary MR cases. However, the likelihood of a successful and durable repair is dependent on the underlying aetiology and the experience of the surgeon. Successful repairs are most likely in isolated posterior leaflet prolapse, with experienced centres boasting a near 100% repair rate with low early mortality (<1%) and reoperation rates (97). Experienced centres state successful repair is probable, with the use of varying surgical techniques, in >98% with PMVL prolapse, in >95% with AMVL prolapse, annular dilatation or commissural leaflet prolapse and 70-80% in those with leaflet restriction/small leaflets or annular calcification (96). However, early mortality,

recurrent MR and re-operation rates are often greater in those with AMVL or bi-leaflet prolapse with studies reporting varying early mortality rates. Some boast low early mortality (<1%) (98, 99), others, such as Castillo *et al* demonstrated 4.8% early mortality in AMVL prolapse patients, however, the study results may be biased by low numbers (n=48) in this group (97). Seeburger *et al* also demonstrated greater early mortality risk in AMVL/Bi-leaflet prolapse patients. The study was performed in a high-volume expert centre, using minimally invasive techniques, the 30-day mortality was 1.5%, 2.6% and 2.2% for PMVL, AMVL and bi-leaflet prolapse respectively (100). Recurrence of MR and reoperation rates are similarly higher in those who undergo MVr for AMVL/bi-leaflet prolapse (99, 101). The most significant impact on the success of mitral valve repair is surgeon experience, with a clear link between surgeon experience and outcome (102, 103). Therefore, reference centres of excellence for mitral valve repair have been developed. These centres must perform >50 MVr operations per year with >25 per specialist surgeon per year. Repair success rates must be >95% and operative mortality <1% (11). In addition to reference centres being created to improve outcomes, the use of minimally invasive surgery and robotic surgery has also developed to improve outcomes. Minimally invasive surgery has longer cardiopulmonary bypass, crossclamp and overall procedure times than conventional mitral surgery via sternotomy, however despite this it can offer equivalent success of repair, stroke rates and early mortality rates. Importantly, minimally invasive surgery results in reduced intensive care, hospital admission and recovery time as well as boasting preferred cosmetic results (104, 105).

1.1.4.2 MV replacement

As per current guidelines the contemporary mitral valve replacement is reserved for those unlikely to achieve a successful durable repair (1, 39), causing a significant reduction in MVR being performed in the developed world. MVR is utilised more often in patients with previous cardiac surgery, advanced age, LV dysfunction (LVEF<45%), mitral calcification, retraction or tethering of the PMVL or

in AMVL prolapse (with ≥2 segments affected)/Barlow's disease and used by surgeons with less experience (96).

Mitral valve replacement can be performed using either mechanical or tissue prosthesis. Mechanical prosthesis are robust with an extremely low possibility of structural failure, but necessitate life-long anticoagulation, with which come associated bleeding risks (106). Prosthetic valve thrombosis is more common in mechanical valves, most obviously in cases of suboptimal anticoagulation and mechanical valves are not immune to developing valve dysfunction from annular pannus formation, which may necessitate re-operation if significant (107). Despite this, mechanical valves are more robust than biological prosthetics with a lower need for re-operation (108). A bio-prosthetic valve is indicated if there is significant bleeding risk from anticoagulation, prior mechanical valve thrombosis despite adequate anticoagulation, in young women considering pregnancy or patients with life expectancy presumed to be less than presumed durability of tissue valve (1, 109). Historic randomised controlled trials comparing mechanical and tissue prosthesis' concur that mechanical valves result in an increased risk of bleeding and stroke, whilst tissue valves suffer from structural valve deterioration resulting in increased reoperations, with no overall significant difference in long-term mortality (110, 111). This finding remains true in modern studies (108). The age cut off at which to start offering tissue replacement valves is controversial, but decreasing with the advent of improved bio-prosthetics. At present, the ESC guidelines advise considering the use of mechanical mitral valves in patients <65years old, but advise to base the decision on an informed discussion with each individual regarding the risks/benefits (1).

Historically MVR involved transection of the chordae tendinae which resulted in a decrease in post-operative LVEF. Modern surgical techniques with MVR utilise chordal preservation to preserve the subvalvular apparatus which results in better preservation of LVEF (112-114). Chordal preservation can be partial or complete, with full perseveration of the subvalvular apparatus providing superior cardiac reverse remodelling (115).

1.1.4.3 MV repair vs replacement

To date, no randomised controlled trials comparing the outcomes of MVr and MVR for the treatment of primary MR have been undertaken. Numerous studies have been performed to observe outcome differences between MVR and MVr, the majority of which were performed before the routine use of chordal preservation techniques with MVR or poorly document its use (116-121). Meta-analysis of studies inclusive of concomitant coronary artery bypass grafting (CABG) demonstrate superiority in MVr over MVR in terms of reduced operative and long term mortality (121). Indeed, studies comparing MVr vs MVR in purely isolated valve disease (no concomitant CABG) also prefer MVr demonstrating lower operative and long term mortality (120, 122, 123). Importantly, MVR is commonly used in patients with more complex mitral valve disease, advanced age, reduced LVEF and worse NYHA class, naturally resulting in a higher risk group pre-operatively than those referred for MVr (123). Studies utilising propensity matching in an attempt to overcome these biases present conflicting results. Gilinov *et al* found no significant difference between long term survival and freedom from re-operation between propensity matched MVr and MVR with chordal preservation groups to treat degenerative MR (123). Although, Lazam *et al* found lower operative mortality, better long term survival and fewer valve related complications post MVr than MVR when treating MR secondary to a flail leaflet, but the use of chordal preservation techniques with MVR was not clearly documented in this study, potentially biasing results (124). Interestingly, a randomised trial comparing MVr vs MVR with chordal preservation in severe ischaemic MR has been performed, demonstrating no significant difference in survival or left ventricular reverse remodelling at 2-years but with greater recurrent MR in the repair group resulting in more heart failure related adverse events and hospital admissions (125). Additionally, results from studies assessing cardiac reverse remodelling also demonstrate the importance performing chordal preservation with MVR. In echocardiographic studies comparing cardiac reverse remodelling between MVr/MVR, when chordal preservation is not used, MVr demonstrates superiority (117, 118), however, when chordal preservation is used with MVR, cardiac reverse remodelling is comparable between the surgical techniques (126, 127). These

findings are important as cardiac reverse remodelling is widely accepted as associated with more favourable prognosis in a wide variety of cardiac disease (128, 129). Therefore MVr/MVR comparative studies predating routine use of chordal preservation with MVR may bias the results in favour of MVr being superior.

A frequent compared variable between MVR and MVr is the reoperation rate. Studies in primary MR report varying re-operation rates with some demonstrating higher reoperations after MVr (especially post AMVL repair) (130), others higher reoperations post MVR (124), but the majority demonstrate no significant difference between the two surgical options (120, 123). In elderly patients, numerous studies (with mixed primary and secondary MR aetiologies) show no reoperations being required post MVR, with a variable rate of reoperations post MVr (1.4-6.1%) (122, 131); despite this no statistical difference was found. Silaschi *et al* similarly demonstrated statistically comparable rates of re-operation in elderly mixed aetiology MR patients undergoing MVR (2.5%) and MVr (2.3%); all reoperations required on replacements were on bio-prosthetic valves (132).

As demonstrated, the vast majority of MVr vs MVR comparative studies utilise ‘freedom from re-operation’ as an endpoint, however this does not take into account all recurrent MR. Indeed, numerous patients who eventually develop significant MR may be deemed too high risk for a re-operation resulting in a lower re-operation end-point frequency and biased results. Recurrent MR post MVr is not uncommon with variable frequencies reported. Grapsa *et al* describes recurrent mild-mod MR in 23.8% of patients within 6 months (133), Chan *et al* describe recurrent moderate MR (2+) in 5.7% of patients within 3.1±2.5years (134), Kim *et al* reported residual moderate-severe MR in 16.8% at 8.7±5.6years (135) and David *et al* reported recurrent moderate-severe MR of 12.5% at 20 years (136).

In summary, the MVR vs MVr debate is ongoing. Current evidence supports MVr as the first line surgical treatment for primary MR, especially when performed in an expert ‘reference’ centre. However, as the MVR cohort is routinely higher risk, this can bias studies towards demonstrating MVr superiority. Additionally, given surgeon experience/operation volume has a significant impact on MVr outcomes

(137), there could theoretically be a similar effect on MVR outcomes. As per current guidance (1, 39), MVR is routinely performed in lower quantity than MVr, theoretically creating an un-explored bias. Without a randomised trial comparing the two procedures using modern techniques in primary MR, the question will not be addressed. However, given current evidence, such a trial could currently be deemed unethical and therefore rigorous hypothesis-generating observational studies are required first.

1.1.4.4 Percutaneous MV interventions

Mitral valve surgery, with repair when feasible, is currently recommended 1st line treatment for mitral regurgitation when indicated (1, 39). However a large percentage of severe MR patients, even though symptomatic, get declined surgical intervention as they are deemed too high risk. Surgery is often declined due to advanced age, severe LVSD or multiple co-morbidities, with one study finding 49% of severe MR patients declined surgery (138). Percutaneous interventions have emerged as a treatment option for this high risk cohort of patients. Multiple percutaneous options exist including edge-edge repair with the MitraClip^{TM} or PASCAL system, transcatheter mitral valve implantation (TMVI), transcutaneous mitral annuloplasty or percutaneous Neochord placement (139).

1.1.4.4.1 Percutaneous edge-to-edge repair

Percutaneous edge-to-edge repair can be performed using the MitraClip^{TM} or PASCAL systems. The MitraClip^{TM} device procedure was designed to copy the central double orifice surgical repair technique initially developed by Alfieri *et al* in 1991, which involved suturing the free edges of the leaflets at the site of regurgitation and was designed as a simple solution for complex lesions (140).The original MitraClip^{TM} system is used via a trans-septal approach to attach a clip device, with a tri-axial catheter system, which grasps the mitral leaflet edges to create a double orifice (141). Newer designs of the MitraClip^{TM} system have followed with the MitraClip^{TM} NT and MitraClip^{TM} XTR (Figure 1-4), the latter

designed with longer arms to facilitate grasping of the leaflets and assist in valves with large coaptation defects (139, 142). Safety of the MitraClip™ system in treating MR was initially demonstrated in the EVEREST (Endovascular Valve Edge-to-Edge Repair Study) trial, in which 107 patients had low mortality and morbidity rates and acute MR reduction (64% discharged with ≤1+ MR severity) in the majority of cases (143). Subsequently, the EVEREST II trial randomised patients with severe MR as a result of mal-coaptation of the A2/P2 scallops, with LVEF>25%, who were deemed suitable for mitral valve repair or replacement to receive either MitraClip™ or conventional mitral valve surgery. The 5-year follow up data demonstrated greater residual MR (3+/4+ MR) and higher rates of subsequent surgery in the MitraClip™ group but a non-significantly lower rate of mortality at 5-years than conventional surgery (144). Both EVEREST trials (I&II) consisted mainly of degenerative MR patients with 93% and 74% in EVEREST I and II respectively (143, 144). The MitraClip™ has since gained greater clinical use in HF patients with secondary MR and has been investigated further in this cohort in the form of two randomised-control trials. The Cardiovascular Outcomes Assessment of the MitraClip™ Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT) trial demonstrated reduced heart failure hospitalisation and mortality in patients with heart failure and moderate-severe or severe secondary MR treated with MitraClip™ and optimal medical therapy compared with those treated with optimal medical therapy alone (145). In contrast, the MITRA-FR study demonstrated no difference in primary endpoints (all cause death or HF hospitalisation) between the MitraClip™ and optimal medical therapy groups (146). The contrasting results are likely attributable to differing inclusion criteria. Both studies recruited patients with heart failure with reduced ejection fraction (ischaemic or non-ischaemic cardiomyopathy) and secondary MR. MITRA-FR recruited patients with LVEF 15-40% and at least moderate secondary MR (EROA >20mm^2, MR-Rvol >30ml). COAPT inclusion criteria was stricter with better LVEF (20-50%), worse MR severity (EROA> 30mm^2 and RVol >45ml) and excluded patients with pulmonary hypertension, moderate/severe RV dysfunction or significant LV dilatation (LVESD >70mm). Recent observations comparing the studies highlight the importance of ensuring only selected patients (as per the

COAPT inclusion criteria) with secondary MR receive MitraClip™ treatment to ensure prognostic benefit (147).

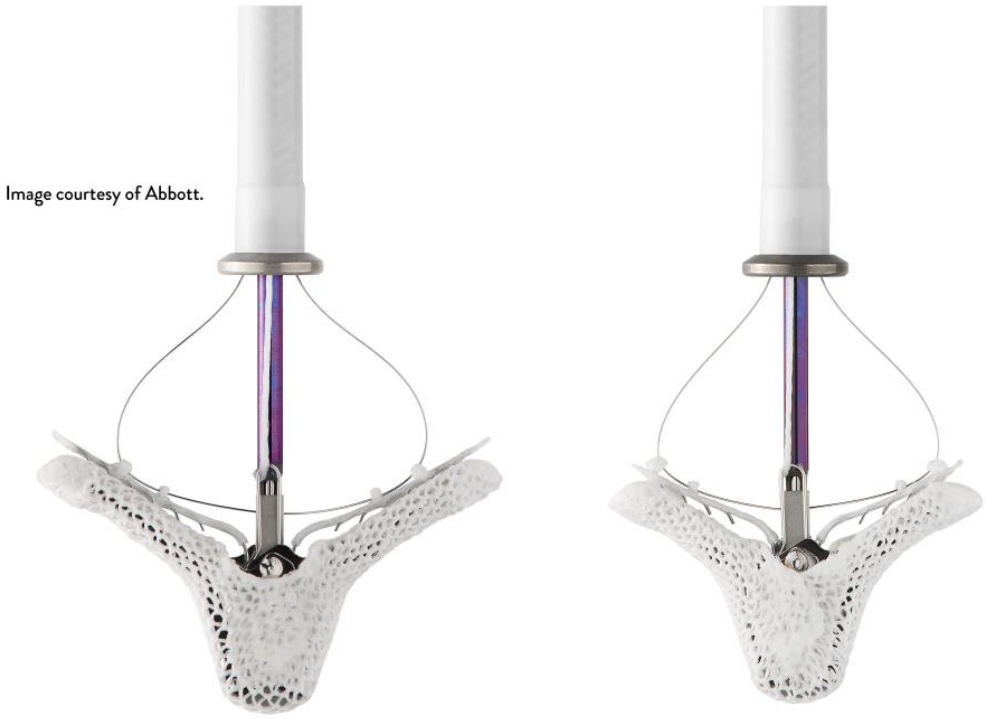


Figure 1-4 MitraClip™ NTR & XTR side by side (image reproduced with permission from Abbot)

The Edwards PASCAL transcatheter mitral repair system is another percutaneous device available to perform edge-to-edge repair. The device was designed to overcome some of the limitations noted with the original MitraClip™ system and therefore was designed to simplify left atrial navigation, use a central spacer to improve reduction of MR, and allow for independent leaflet grasping. The initial multicentre study using the PASCAL system boasted high technical success rates and MR severity reduction (148) and a subsequent multicentre trial demonstrated reduced MR regardless of aetiology and improved quality of life, exercise capacity and functional status at 30 days (149) with residual MR ≤2+ in all patients and MR ≤1+ in 82% at 1-year follow up (150).

1.1.4.4.2 Transcatheter mitral valve implantation (TMVI)

After the successful development and widespread clinical use of transcatheter aortic valve implantation (TAVI) in high risk aortic stenosis patients (151) and effective use of valve-in-valve TAVI for failed aortic bioprosthesis (152) the progression to TMVI was inevitable. In clinical practice TMVI is often reserved for annuloplasty ring failure (153), failed bioprosthesis (154, 155) or degenerative mitral valve disease with mitral annular calcification (156). Various emerging transcatheter mitral valve implantation devices exist that are either self-expanding (157-159) or balloon expandable (160, 161) and implanted by a trans-apical (157-159, 161) or trans-septal approach (157, 160, 161). Outcomes from the transcatheter mitral valve replacement multicentre registry, including 521 patients (60.5% trans-apical access, 90% used SAPIEN valves) that underwent TMVI, demonstrate overall excellent technical success in 87% of cases but differing outcomes depending on the underlying rationale for TMVI. Those undergoing TMVI for bio-prosthetic valve failure demonstrated superior outcomes. Whilst TMVI used in failed mitral annuloplasty repairs were prone to significantly more recurrent MR and increased requirement for second valve implantation. Finally, TMVI used to treat MR as a result of mitral annular calcification more frequently suffered left ventricular outflow tract (LVOT) obstruction and higher 30-day and 1-year all-cause mortality (162).

1.1.4.4.3 Transcatheter direct annuloplasty mitral valve repair

Multiple transcatheter devices have been developed to mimic the standard surgical mitral valve repair technique that utilises annuloplasty (139), which is especially important in functional MR where annular dilatation can be a fundamental pathological cause (163). Transcatheter mitral annuloplasty can be performed directly or indirectly.

Indirect transcatheter annuloplasty aims to reduce MR by altering the proximity of the coronary sinus to the posterior mitral valve annulus. The Carillon mitral contour system uses a distal anchor deployed deep in the coronary sinus to apply

backward traction, guided by echocardiography and fluoroscopy, to alter the mitral annulus shape and reduce MR. A proximal anchor is then deployed near the coronary sinus ostium. Subsequent coronary angiography is performed to ensure no coronary artery compromise (due to the proximity of the circumflex artery to the coronary sinus) which necessitates recapture/removal of the device and can exclude patients from this approach (164). Two single arm trials (TITAN I & TITAN II) demonstrated that the device reduced MR severity, HF admission and produced favourable LV reverse remodelling (164, 165). A subsequent sham randomised control trial (REDUCE-FMR) in 120 patients with functional MR and reduced ejection fraction (87 treatment arm, 33 sham control arm) demonstrated reduced MR-Rvol and LV volumes in the treatment group compared with the sham control group (166).

Direct transcatheter annuloplasty systems have been developed more recently and attach a ring or band directly to the mitral valve annulus under echocardiographic or fluoroscopic guidance. Although other devices exist (167, 168), to date, the Cardioband system has the most published data in clinical use. The Cardioband device is implanted via a transeptal approach with the ring positioned at the atrial side of the mitral valve annulus. Multiple anchors are used with the first and last deployed in the lateral and medial commissures respectively with intermittent anchors placed at short intervals in-between (169). In a recent multi-centre study in functional MR patients, 123 patients treated with the Cardioband device and 455 patients treated by MitraClip^{TM} were propensity matched into two groups of 93 patients. Both device treatments resulted in reduced MR and heart failure symptoms but there were greater improvements in functional class and lower all-cause rehospitalisation and all-cause mortality rates in those treated with the Cardioband device (170).

1.1.4.4.4 Neochord procedure

Transapical off-pump mitral valve repair with neochord implantation, also known as the Neochord procedure, uses the NeoChord artificial chordae delivery system (NeoChord, Inc., St. Louis Park, MN, USA) to place expanded

polytetrafluoroethylene sutures as replacement neochordae to treat degenerative mitral regurgitation. The procedure is performed under general anaesthetic on a beating heart using transoesophageal guidance and doesn't require cardiopulmonary bypass (171, 172). A multicentre study in 213 patients demonstrated procedural success in 96.7% of cases. The underlying aetiology of primary mitral valve disease had a significant effect on the composite end-point at 1 year which comprised of freedom from mortality, severe mitral regurgitation, stroke, rehospitalisation, re-intervention and a decrease of at least 1 New York Heart Association (NYHA) functional class. Patients with isolated central PMVL prolapse had superior outcomes with 94 ± 2.6% reaching the composite end-point, compared with 82.6 ± 3.8% and 63.6 ± 8.4% in patients with multi-segment PMVL disease and anterior/bi-leaflet mitral valve disease respectively. Therefore careful patient selection is important for optimal outcomes (173).

1.1.4.4.5 Combined percutaneous procedures

Evidence from conventional surgical intervention suggests combined annuloplasty and leaflet repair provides superior outcomes to valve repair or annuloplasty alone (174-176), therefore similar outcomes may be found by combining percutaneous procedures. Indeed, combined MitraClip^{TM} with transcatheter mitral annuloplasty have been reported (177, 178). Given the wide range of percutaneous techniques available the ability to be able to combine techniques/tailor the techniques used to individual pathology is inviting, but further research is clearly required using combined techniques to assess which patients will benefit.

1.1.5 Mitral regurgitation: summary

Mitral regurgitation is a common but complex disease, with multiple aetiologies and variables that effect prognosis and treatment outcomes. Accurate cardiac imaging is essential to assist optimal management. TTE provides a widely available and cheap first line investigation, but has limitations with regards body habitus and often utilises a semi-quantitative assessment of MR as quantitative assessment relies on geometric assumptions and careful Doppler alignment which can reduce accuracy. Therefore, in borderline cases additional imaging can be important to assist decision making. Exercise stress TTE can provide prognostic information not present at rest to assist decision making, but can be similarly limited by poor acoustic windows and suboptimal MR quantification. TOE overcomes the issue of acoustic windows and allows unparalleled assessment of valve morphology, but is invasive and still limited by geometric assumptions to quantitate MR.
Consequently, CMR has developed as the reference standard in MR quantification with superior accuracy, reproducibility and prognostic ability compared to TTE. However, CMR assessment of valve morphology is inferior to good quality echocardiography owing to poorer spatial and temporal resolution. Therefore a multi-modality approach is essential to provide a comprehensive assessment and guide optimal management. Surgical intervention is the gold standard treatment in primary MR. MVr is recommended when feasible over MVR, on the basis of non-randomised trials, however further research is warranted in light of recent studies. Excitingly, numerous percutaneous mitral valve procedures have developed to treat patients not suitable for surgical intervention and suggest a future where patients may benefit from combined techniques individualised to best treat their disease.

1.2 Exercise Cardiovascular Magnetic Resonance: development, current utility and future applications

Stress cardiac imaging is the current first line investigation for coronary artery disease diagnosis and decision making and an adjunctive tool in a range of non-ischaemic cardiovascular diseases. Ex-CMR has developed over the past 25 years to combine the superior image qualities of CMR with the preferred method of exercise stress. Presently, numerous exercise methods exist, from performing stress on an adjacent magnetic resonance imaging (MRI) compatible treadmill to in-scanner exercise, most commonly on a supine cycle ergometer. Cardiac conditions studied by Ex-CMR are broad, commonly investigating ischaemic heart disease and congenital heart disease but extending to pulmonary hypertension and diabetic heart disease. There follows an in-depth assessment of the various Ex-CMR stress methods and the varied pulse sequence approaches, including those specially designed for Ex-CMR. Current and future developments in image acquisition are highlighted, and will likely lead to a much greater clinical use of Ex-CMR across a range of cardiovascular conditions.

1.2.1 Background

Stress testing can be a pivotal tool for the diagnostic and prognostic assessment of cardiovascular disease. Historically for coronary artery disease (CAD), treadmill electrocardiography (ECG) was the reference standard (179, 180). However, the use of stress cardiac imaging for exercise testing has significantly improved the diagnostic accuracy for CAD detection compared to exercise ECG alone (181-186). Thus stress imaging is now the preferred investigation for CAD diagnosis in intermediate risk patients and a useful tool for prognostication and decision making (187, 188). CMR has several well established benefits over alternative imaging modalities, allowing a non-invasive comprehensive multi-parametric assessment, with few limitations from body habitus, no ionizing radiation (189), and is the reference standard for bi-ventricular volume and functional assessment (51-53).

Pharmacological stress CMR has become widely utilised clinically, demonstrating superiority over myocardial perfusion scintigraphy by single photon emission computed tomography (MPS-SPECT) in the diagnosis (190) and prognosis of CAD (191) and recently, a lower incidence of revascularization and non-inferiority in major adverse cardiac events compared to CAD management guided by coronary angiography with fractional flow reserve (192). However, pharmacological stress has more adverse events than exercise stress, as demonstrated in stress echocardiography (80, 82), contraindications and side effects patients may not tolerate (193) and does not replicate the neurohormonal and haemodynamic changes associated with physical exercise. As such, current guidelines advise physical exercise as the preferred method for stress imaging, when feasible (83, 84). Exercise imaging studies primarily focus on CAD, however exercise testing is an important decision making tool in numerous cardiac diseases including valvular heart disease (37) and congenital heart disease (194).

Despite the advantages of CMR as a modality and physical exercise advised first line, Ex-CMR is not widely used clinically. Limitations include difficulty with image acquisition and quality, the expense of commercially available MRI compatible exercise devices (195) and that exercise testing is technically more difficult than administering pharmacological stress (196). This section will focus on the recent development of Ex-CMR as a technique, its current utility and challenges, and its potential future applications and technical developments.

1.2.2 Exercise CMR – methodology and development

Ex-CMR is performed either by exercising outside the scanner bore on a MRI compatible adjacent treadmill (197) or by exercising in the MRI scanner, most commonly using a supine cycle ergometer. Exercise on a MRI compatible adjacent treadmill, utilising a Bruce protocol treadmill test, benefits from the safety of 12-lead ECG monitoring, essential for identifying ECG changes which may prompt test termination, but with the limitation of requiring rapid transfer to the MRI isocenter for post stress imaging. In-scanner Ex-CMR overcomes this limitation, as exercise can be performed in the scanner bore, with imaging performed during exercise or a

brief cessation of exercise. However, CMR scanning during exercise creates several issues including increased physical and respiratory motion creating artefacts, ECG gating issues and safety cannot be monitored by 12-lead ECG (198). Indeed accurate ST segment monitoring is not feasible within the MRI scanner bore due to the magnetohydrodynamic effect distorting the surface ECG (199). ECG gating issues can occur at maximal heart rates and during exercise. At maximal heart rates this can be overcome with real time imaging after exercise cessation, as utilised in treadmill Ex-CMR (200), or with ungated real time imaging during maximal supine bicycle exercise (198). Exercise inherently causes movement, which can result in image acquisition away from the initial planned slice location. Movement can be reduced physically by using straps around the chest and anterior coil, and by counselling/training the patient. However, meticulous image planning is essential to ensure appropriate stress slice localisation. Short axis cine imaging, for ventricular volumetric analysis, should be planned with sufficient slices beyond the base and apex, to account for movement. Repeating left and right ventricular outflow tract views after/during exercise, with free breathing imaging, immediately prior to phase contrast imaging of the aorta or main pulmonary artery allows re-planning to account for movement that may have occurred whilst performing in-scanner exercise. Respiratory navigation can be performed to accommodate for respiratory motion and can be performed retrospectively with ungated real time CMR imaging by manually ‘gating’ respiration using a plethysmograph trace (198).

Numerous exercise CMR studies have been performed using varying methods, including treadmill exercise, supine cycle ergometer or supine stepper-stress, upright cycle ergometry in an open magnet, isometric handgrip exercise (IHG) and prone exercise using either knee flexion or extension with resistance from cables or non-ferromagnetic weights. Similar to exercise echocardiography (80), the range of applications of Ex-CMR extends beyond CAD to a wide range of cardiac conditions (80). Each exercise method has inherent benefits and weakness (Table 1-6). Treadmill exercise, to date, has demonstrated the most clinical utility, being the only validated method for ischaemia detection, however, in-scanner supine

cycle ergometer exercise has numerous publications in a broader range of cardiac conditions. Each exercise method will be reviewed including its benefits, limitations, published applications and the technological and imaging sequence developments that have occurred to overcome the described issues of performing Ex-CMR.

Table 1-6 Characteristics and benefits of the varying exercise modalities used in exercise CMR

Exercise type		Commonly published applications	Max exercise intensity*	Strengths	Weaknesses
Outside scanner	Treadmill	Ischaemia testing (Regional wall motion & perfusion)	Maximal	Patients better achieve maximal intensity Diagnostic 12 lead ECG performed during Treadmill test provides separate prognostic data Simultaneous Maximal oxygen uptake testing feasible Most natural and tolerated form of exercise	Post stress imaging allows recovery of HR before imaging Logistically difficult to image at multiple exercise intensities
In-scanner Exercise	Upright cycle ergometer	Flow assessment	Light	Allows imaging during exercise Allows imaging to multiple exercise intensities Only modality with upright in-scanner exercise Less claustrophobia in open magnet scanner	No 12-lead ECG monitoring/ST segment analysis Uses open magnet scanner: low field strength (low SNR), limited availability, CMR feasible but non-standard. Minimal published studies
	Supine Cycle ergometer	Ventricular volumes Flow assessment	Maximal	Allows imaging during exercise Allows imaging to multiple exercise intensities Maximal in-scanner exercise achievable	No 12-lead ECG monitoring/ST segment analysis Cycling can be restricted by magnet bore diameter
	Supine stepper ergometer	Ventricular volumes Flow assessment	Vigorous	Allows imaging during exercise Allows imaging to multiple exercise intensities Less leg restriction than cycle ergometer	No 12-lead ECG monitoring/ST segment analysis Lower intensity exercise than cycle ergometer
	Prone exercise	Spectroscopy	Light-Moderate	Allows imaging during exercise	No 12-lead ECG monitoring/ST segment analysis Unconventional form of exercise Only modest exercise feasible Logistically difficult to increase resistance
	Isometric Handgrip	Spectroscopy /Coronary endothelial function	Very-light	Allows imaging during exercise Stable stress HR Minimal movement & no magnet bore restriction	No 12-lead ECG monitoring/ST segment analysis Atypical form of exercise Limited increase in HR

* Exercise intensity as defined by the American Society of Sports Medicine guidelines (201). Abbreviations: HR, heart rate.

1.2.3 Treadmill exercise CMR

Directly analogous to treadmill stress echocardiography, treadmill Ex-CMR is performed to achieve the required exercise intensity/THR. The patient is then rapidly transferred into the MRI scanner for post stress imaging. Treadmill Ex-CMR has progressed from exercising outside the scanner room (202), to the development of an MRI compatible treadmill to allow exercise to take place inside the scanner room (203) and eventually performed adjacent to the MRI scanner (197) (Figure 1-5). For ischaemia studies, this progression has reduced the 'cooling off period' from peak stress to image acquisition, as even a 60-90 second delay in performing stress echocardiography image acquisition, has demonstrated recovery of ischaemic regional wall abnormalities and thus decreases the sensitivity of ischaemia detection (204, 205). Numerous studies in exercise echocardiography have demonstrated the differences between peak and post-stress imaging, specifically demonstrating that peak stress imaging has superior sensitivity and accuracy at detecting ischaemia than post stress imaging (204, 206-209). A direct 'head-to-head' comparison in stress echocardiography demonstrated that peak stress supine bicycle echocardiography was superior to post stress treadmill echocardiography in ischaemia detection (210). Consequently, stress echocardiography guidelines recommend post stress imaging be accomplished in under 60 seconds (196). However, as CMR can detect ischaemia by assessing myocardial perfusion in addition to assessing wall motion abnormalities, treadmill Ex-CMR may be less time sensitive post exercise cessation than treadmill echocardiography. Varying transfer times have been achieved in treadmill Ex-CMR studies (Table 1-7) (197, 200, 202, 203, 211-214). Since progression to an MRI compatible treadmill adjacent to the scanner, all studies demonstrate scan initiation in under 30 seconds (with the exception of La Fountain *et al* in which removal of the face mask assessing oxygen uptake prolonged transfer time (211)) and cine imaging completion in under 60 seconds (212-214).

Figure 1-5 MRI compatible scanner adjacent treadmill

MRI compatible scanner adjacent treadmill, developed and utilised in ischaemia studies by the Ohio State University Research group (197), reduces transfer times for post stress CMR imaging, whilst still allowing a diagnostic 12-lead ECG treadmill test and a simultaneous maximal oxygen uptake test, if required.

Table 1-7 The transfer times and resultant imaging heart rates in treadmill exercise CMR studies

					Time (s) from exercise cessation to stress CMR:					
	Patient population	n=	Age	Treadmill location	Start	Cine image End	Perfusion Image end	Peak HR	Imaging HR	CMR finish HR
Rerkpattanapipat (2003) (202)	Patients referred for angiography	27	62±11	Outside scanner room	NS	61 ± 24	N/A	130 ±20 bpm	113 ±16 bpm	NS
Jekic (2008) (203)	Healthy volunteers	20	39±15	Scanner room corner	30 ± 4	45 ± 4	57 ± 5*	98 ±7% THR	84 ±11% THR	NS
Raman (2010) (200)	Patients referred for MPS-SPECT	43	54±12	Scanner room corner	42± 5	68 ± 14	88 ± 8	93 ±9% THR	74 ±10% THR (cine)	NS
Foster (2012) (197)	Healthy volunteers	10	23-67	Scanner adjacent	24± 4	40 ± 7	50.5± 9	98 ±8% THR	86 ±9% THR	81±9% THR
Thavendiranathan (2014) (213)	Healthy volunteers	28	28±11	Scanner adjacent	21± 2	41 ± 4	N/A	173bpm (146-196)	148±14 bpm	NS

Sukpraphrute (2015) (214)	Patients with known or suspected CAD	115	59±13	Outside scanner room	NS	<60s**	N/A	88±12% THR	NS	NS
Lafountain (2016) (211)	Athletes	10	26±5	Scanner adjacent	36±4***	NS	N/A	>95% THR	87%	NS
Raman (2016) (212)	Patients referred for MPS-SPECT	94	57±11	Scanner adjacent	25 ± 13	46 ± 16	87 ± 36	97±10% THR	<u>Cine</u> 83±11% THR <u>Perfusion</u> 76±11% THR	NS

* Time to peak perfusion, ** 100% of patients completed diagnostic imaging in <60s, exact times not specified. *** CPET face mask removal increased transfer time. Abbreviations: BPM, beats per minute; CAD, Coronary artery disease; CPET, cardiopulmonary exercise test; HR, Heart rate; MRI, magnetic resonance; N/A, Not applicable; NS, not specified; N=, Number of patients; MPS-SPECT, Myocardial perfusion scintigraphy Single-photon emission computed tomography; THR, Target heart rat

1.2.3.1 Treadmill Ex-CMR Exercise Protocol

The current treadmill Ex-CMR protocol entails performing initial resting survey imaging and LV cine imaging. The patient is removed from the scanner bore for a supine 12 lead ECG, then transfers to the scanner adjacent MRI compatible treadmill for an initial standing 12 lead ECG and subsequently performs a symptom limited Bruce protocol treadmill test. After achieving THR >0.85 x (220-age), the patient is rapidly transferred to the MR scanner for free-breathing multiplane cine imaging. 0.1mmol/kg gadolinium contrast is injected prior to stress perfusion imaging, after which the MRI scanner table is removed from the magnet bore to allow 6-8 minutes of recovery with 12-lead ECG and blood pressure monitoring. The imaging is completed with rest perfusion and late gadolinium enhanced sequences. (212). This protocol is compared with adenosine/dobutamine pharmacological stress CMR imaging in Figure 1-6 (193, 212, 215).

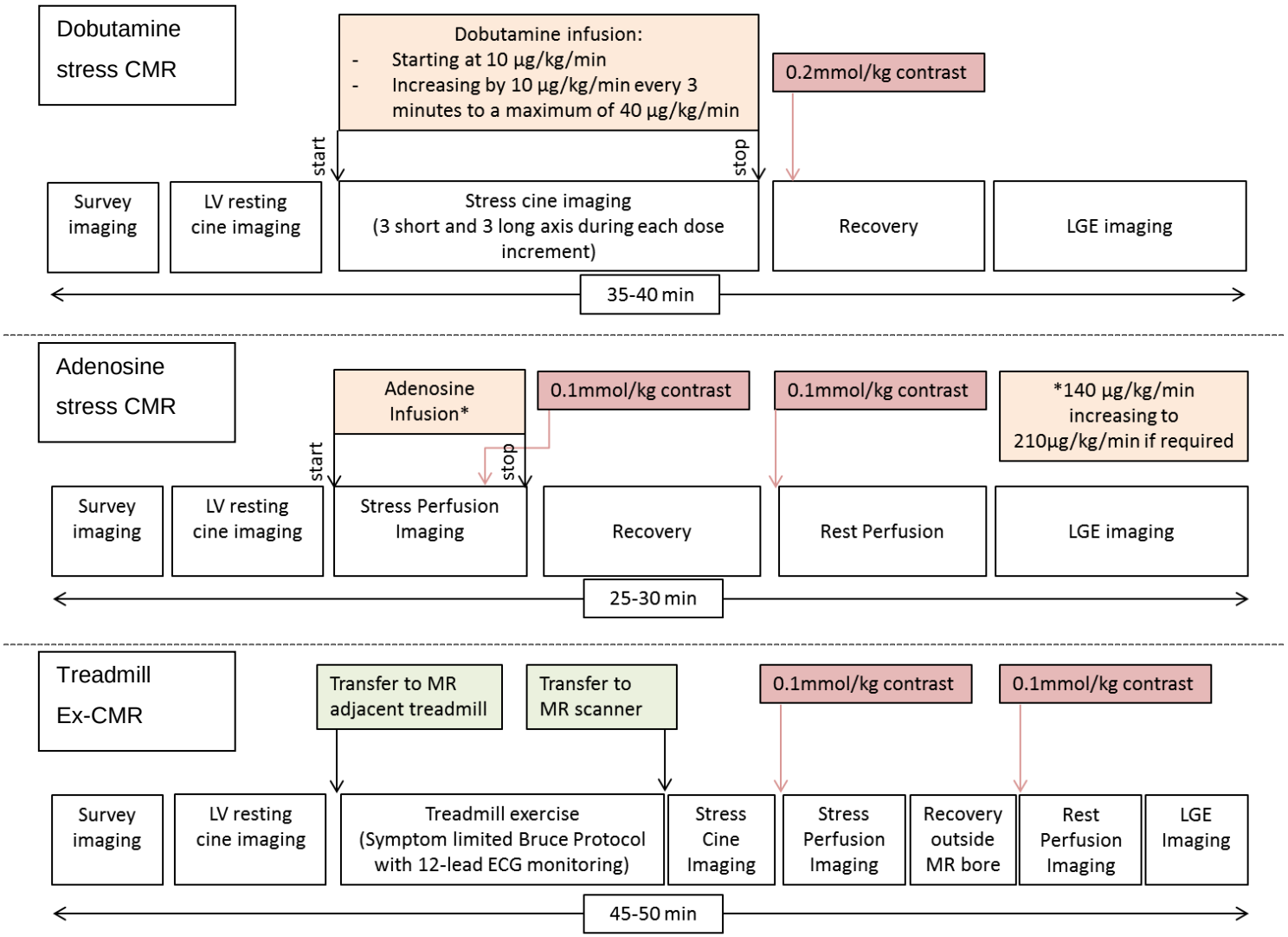


Figure 1-6 Comparison of pharmacological stress CMR using Dobutamine Adenosine or exercise treadmill CMR protocols.

Estimated times of completed protocols may vary and may be dependent on centre experience.

Abbreviations: ECG, electrocardiogram; Ex-CMR, exercise cardiovascular magnetic resonance; LGE, late gadolinium enhancement; LV, left ventricle

1.2.3.2 Treadmill Ex-CMR sequences

CMR imaging sequences used after treadmill exercise have developed, to hasten acquisition and remove breath holding. Initially, retrospectively gated sequences were used with short breath holds to acquire short axis cine imaging for regional wall motion abnormality assessment (202). The use of real time bSSFP imaging with either TSENSE or GRAPPA acceleration, allowed progression to free breathing acquisition of short and long axis left ventricular (LV) cine images for regional wall motion assessment (200, 203, 211-213). Additionally, perfusion imaging has been performed in several studies, after cine image acquisition, using saturation recovery hybrid gradient echo, echo planar imaging (200, 212).

Treadmill stress CMR offers several benefits over other Ex-CMR modalities (Table 1-6). Patients often tolerate treadmill exercise greater than cycling, as it is a more natural form of exercise (216) and some patients are unable to cycle (196). Patients more readily achieve >85% age predicted target heart rate on the treadmill compared to non-weight bearing exercise (210, 217). The treadmill test itself provides diagnostic and prognostic information independent of imaging (200, 218-220) and a traditional maximal oxygen uptake assessment is feasible during treadmill exercise within the MR scanner room (211). Treadmill stress incorporates a 12-lead ECG exercise test, which is diagnostic even on an MR adjacent treadmill, compared with non-diagnostic ECG monitoring performed when exercising inside the MR scanner (221). This monitoring may be vital to assess for ST segment changes or arrhythmias which can be absolute indications to terminate an exercise test during ischaemia testing (222). Therefore treadmill Ex-CMR is arguably the safest Ex-CMR methodology to assess CAD. There are limitations to treadmill Ex-CMR. Imaging at numerous exercise intensities is logistically difficult and post stress imaging restricts the time available before a decline in heart rate, thus limiting applications to those achievable within a few minutes. The transfer process also interrupts the advised post-exercise ECG observation period (222). However, whilst MR stress perfusion is feasible using the supine cycle ergometer in healthy volunteers (223), treadmill Ex-CMR is currently

the only Ex-CMR modality to demonstrate utility in ischaemia detection in CAD patients, with clinical evidence from single and multi-centre studies (200, 202, 212, 214).

1.2.4 In-scanner Exercise CMR

In-scanner Ex-CMR can be performed by supine cycle or stepper ergometer, upright cycling in an open magnet, exercise in the prone position or using isometric handgrip; the strengths and weaknesses of the varying methods are presented in Table 1-6. In-scanner exercise overcomes the main limitation of treadmill Ex-CMR of heart rate (HR) reductions between exercise cessation and image acquisition. Imaging during exercise does however have difficulties. Exercise invariably creates movement, increased respiratory motion and interference to the surface ECG, all of which increase with increasing workload. Movement can be reduced with the use of straps or harnesses, but not entirely, especially at higher levels of exercise. Breath held images can be performed during exercise but are non-physiological and difficult at higher exercise intensities (198) . Imaging during free breathing can cause significant through plane motion, making obtaining reliable flow measurements difficult, with the pulmonary trunk especially challenging due to its short length before bifurcation (224). ECG interference during exercise can create ghosting artefacts with gated images and as previously described, accurate 12 lead ECG monitoring with ST segment analysis cannot be performed during in-scanner exercise (198, 199, 221). Finally, reaching maximal heart rate is more difficult with supine exercise compared with upright exercise; this is well documented in stress echocardiography with comparisons between treadmill and supine cycle exercise (210, 217, 225, 226). One explanation is early termination due to leg fatigue (210, 222), thus maximal oxygen uptake (VO_{2max}) is often 10-20% lower in supine cycle exercise than treadmill exercise. Despite this, evidence from stress echocardiography demonstrates equivalency or superiority in detecting ischaemia over post stress treadmill exercise (210, 217, 225). Indeed, comparatively higher blood pressure attained during supine ergometry (210, 217, 226, 227), results in a similar rate-pressure product to treadmill exercise, such that

target heart rates during supine exercise are generally lower when compared to the same exercise intensity in the upright position. Despite the described difficulties of performing in-scanner exercise CMR, techniques have been adapted, with the use of the supine cycle ergometer, such that it is possible to perform in-scanner Ex-CMR to maximal intensity heart rates with imaging during exercise to assess either bi-ventricular function or great vessel flow (198, 224), but often not both, due to time constraints of scanning at incremental levels during or immediately post exercise.

1.2.4.1 Supine Ergometer Exercise CMR

The first published use of a CMR compatible cycle ergometer was in 1995 using a 0.5T whole body scanner to measure exercise changes in aortic flow (228). Studies utilising commercially produced cycle ergometers followed in 1998 with the use of the Lode BV MRI compatible ergometer (Figure 1-7) on a 1.5T MRI scanner (229). Whilst the majority of Ex-CMR cycle ergometer studies use this system (81, 198, 223, 224, 229-248), some institutions have created custom made MRI compatible cycle ergometers (195, 249, 250). Other approaches include the supine MRI compatible ‘stepper’ ergometer, that utilises an up/down motion, such as the Lode BV up/down ergometer (251-254), Ergospect cardio-stepper (251) and custom built supine steppers as demonstrated in Figure 1-8 (255). Studies using stepper systems report the benefit of reduced upper body motion, thus reduced motion artefact, and less restriction of leg movement compared with cycle ergometers, however no studies directly comparing the ergometers have been performed. Importantly, the up/down motion recruits less muscle mass than the cyclical motion. Thus no study has demonstrated supine ‘stepper’ ergometer Ex-CMR to maximal intensity, as has been demonstrated with supine cycle ergometers (198).

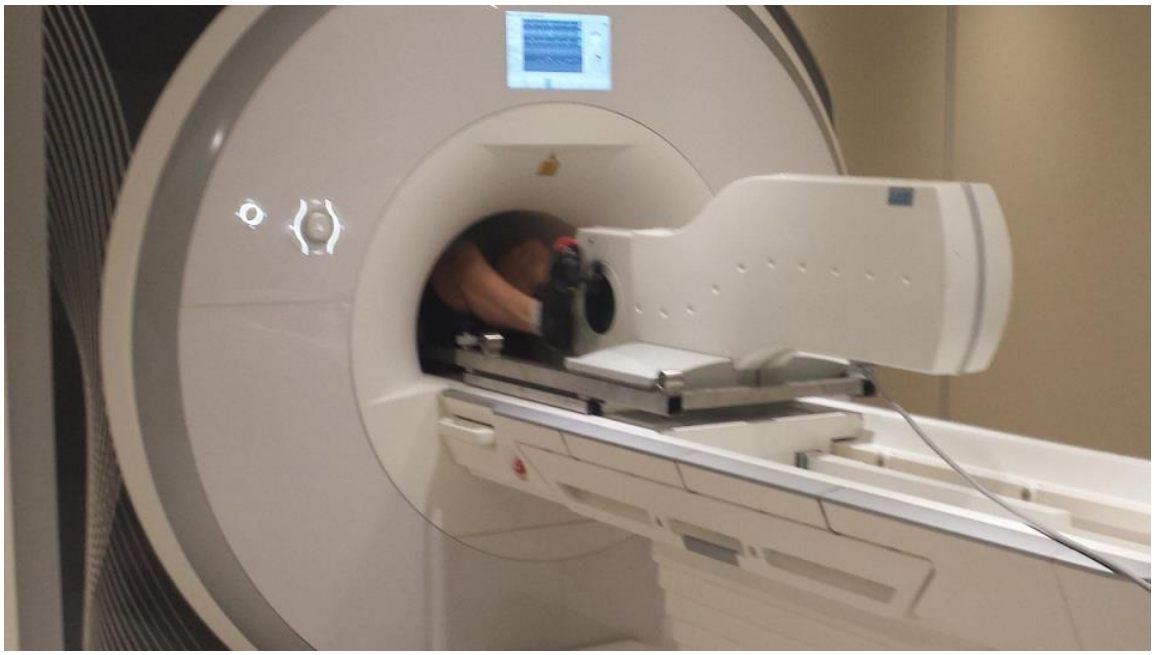


Figure 1-7 Lode BV supine cycle ergometer during in-scanner supine exercise cardiac magnetic resonance

The Lode BV supine cycle ergometer allows in-scanner exercise, up to maximal exercise intensity, during CMR scanning, as demonstrated by La Gerche *et al* (198). The ergometer attaches firmly to the MRI scanner bed by screw attachments and is safe to use in MRI scanners up to 3T. The patients' feet attach into the stirrups and strap securely in place. Resistance can be altered manually in 1-watt intervals. This ergometer is the most utilised modality in Ex-CMR research studies.

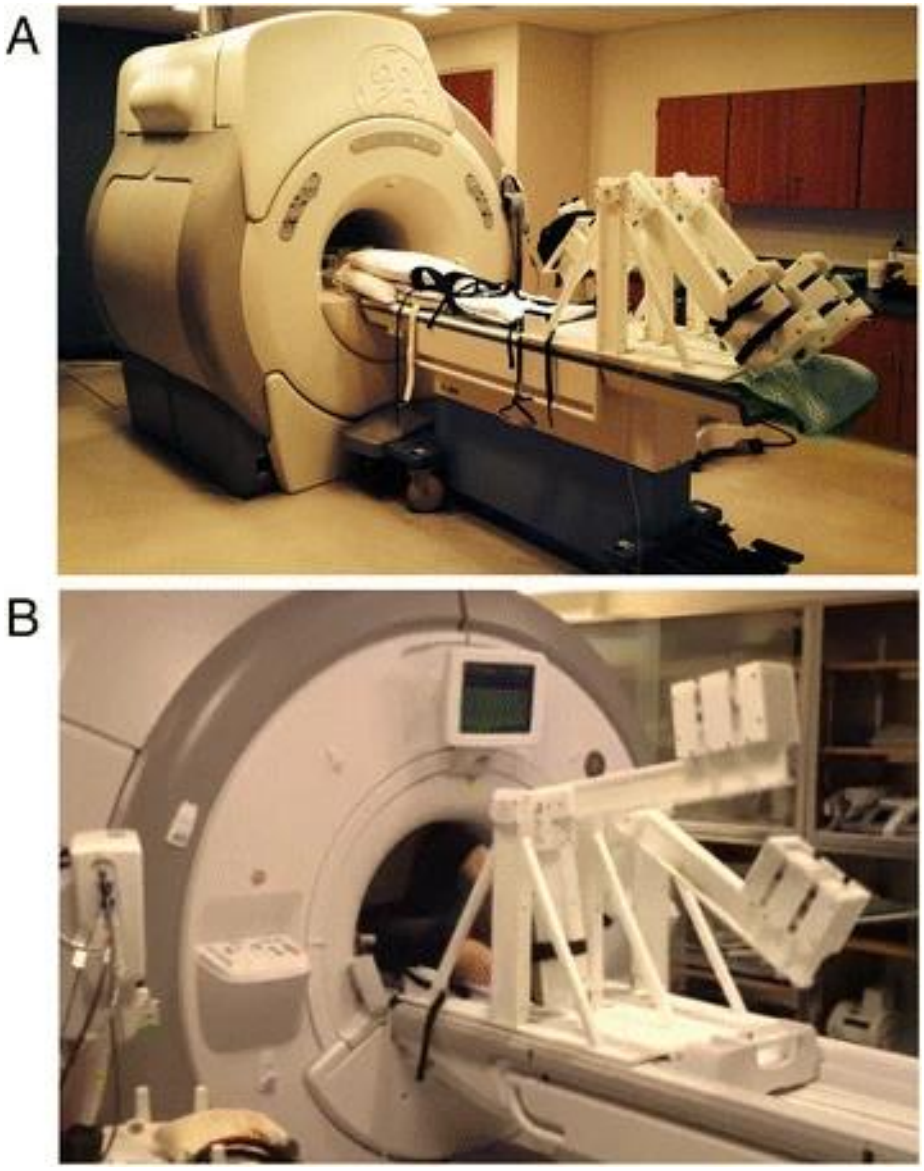


Figure 1-8 Custom supine stepper ergometer.

An example of a supine stepper ergometer utilised in research at the University of Wisconsin (255). A. The ergometer outside the MRI-scanner. B- The ergometer in use. The ergometer allows for exercise via an up/down motion, a technique which is reported to cause less movement artefact than the cycle ergometer at the cost of less muscle mass recruitment and thus lower achievable maximal heart rates.

1.2.4.2 Exercise Protocol

Exercise protocols used with supine cycle ergometer Ex-CMR vary depending upon the aims of the study/investigation. An example protocol is presented in Figure 1-9. The number of stages of exercise is variable depending upon the aims. A typical protocol often entails a period of supine cycling with no resistance (0 Watts) on the ergometer, to allow the patient to accustom to the cycling positon and the advised cadence. This is followed by a graduated increase in resistance, for example by 25 Watts every 2 minutes, until THR is achieved. However, in athletes a faster increase in resistance may be advised. The resistance is then maintained whilst at the specific exercise intensity heart rate. Indeed minute changes in resistance can be made, if required, to ensure tight control of heart rate during scanning. Once THR has been maintained for 60 seconds CMR imaging will commence. After completion of a specified exercise intensity stage, the process of ‘ramping up’ resistance, acquiring a stable THR prior to imaging and maintaining that THR during imaging is repeated for each exercise stage required.

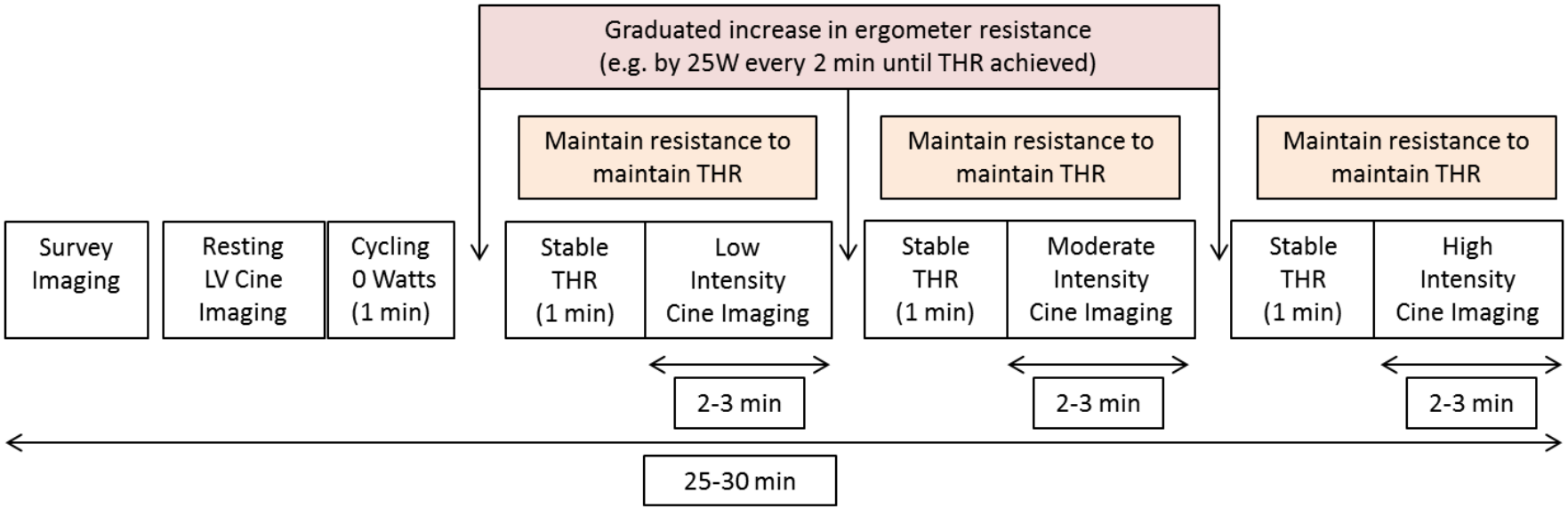


Figure 1-9 Example of supine bicycle Ex-CMR protocol

An example of a supine bicycle Ex-CMR protocol. In-scanner Ex-CMR protocols may vary depending on indication, number of exercise stages required and participant fitness. Participants with superior cardiovascular fitness may benefit from shorter intervals between, or more aggressive, increases in resistance to achieve THR before leg fatigue. Using the Lode BV supine cycle ergometer, small alterations in resistance are possible, which can assist a tight control of THR. Abbreviations: LV, left ventricular; THR, target heart rate; W, Watts.

1.2.4.3 In-scanner ventricular volumetric assessment

Supine ergometer Ex-CMR ventricular volume assessment has progressed from imaging during exercise cessation with breath holding (81, 195, 238-240, 249), breath holding during exercise (250, 251), free breathing with exercise cessation (223, 233, 235), to free breathing during continuous exercise (198, 252). This progression has been due to the use of novel CMR sequences and the progression from the use of retrospective cardiac gating to real-time and un-gated real time techniques to overcome issues with ECG gating.

Initial Ex-CMR studies utilised retrospective cardiac gating with turbo field echo planar imaging (EPI) (81, 238, 239) or b-SSFP sequences (195, 249, 250, 256, 257) to assess biventricular volumes during Ex-CMR. These were not initially feasible with free breathing during continuous exercise. However, recently, Chew *et al* used a free-breathing, multi-shot, respiratory navigated cine imaging method to assess biventricular function during continuous supine Ex-CMR with retrospective cardiac gating. Healthy volunteers exercised to high exercise intensities (mean peak HR= 131bpm) demonstrating excellent intra- and inter-observer reproducibility and highly reproducible Inter-scan LV and RV ejection fraction (93).

Prior to the recent development using retrospective cardiac gating in Ex-CMR by Chew *et al*, published retrospective cardiac gating techniques had not performed image acquisition with free breathing during exercise, this was instead achieved using real time techniques. The seminal real time Ex-CMR study by Lurz et al used a CMR sequence novel at the time (real time radial k-t-SENSE) demonstrating higher temporal resolution than the vendor provided sequences in patients exercised to submaximal intensity (252). Subsequent real-time Ex-CMR studies have utilised alternative techniques to optimise image quality including the use of re-binning, which improved SNR and temporal resolution compared with standard sequences, but suffered from ECG gating artefacts in 2 patients resulting in them being withdrawn from the study (258). Whilst Le *et al* preferred resorting back to

exercise cessation with real time sequences, to overcome ECG interference during Ex-CMR and thus optimise image quality (235).

Reliable biventricular assessment during maximal exercise has been achieved by La Gerche *et al* with the development of an ‘un-gated real time sequence’ (Figure 1-10). Cine images are acquired by an un-gated real-time technique, physiological data is acquired separately, with respiration measured by a plethysmograph attached to the abdomen and ECG recorded via a haemodynamic monitor. Specialized in-house software was then used to retrospectively synchronise the physiological data and cine images. The un-gated technique overcame the issue of excessive ECG artefact encountered during high intensity exercise with the gated sequence on direct comparative assessment. The cardiac output derived by this technique was validated against the direct Fick method with excellent agreement and showed excellent correlation with cardiac outputs on repeat Ex-CMR performed 1-hour later (198). Although major limitations of this approach are the prolonged post processing time and the requirement for bespoke in-house analysis software to synchronize the ECG and respiratory movement with the images, it is the only method to date to allow accurate biventricular quantification during maximal exercise and has since been utilised in a number of clinical studies (231, 232, 234, 241, 244, 245, 248).

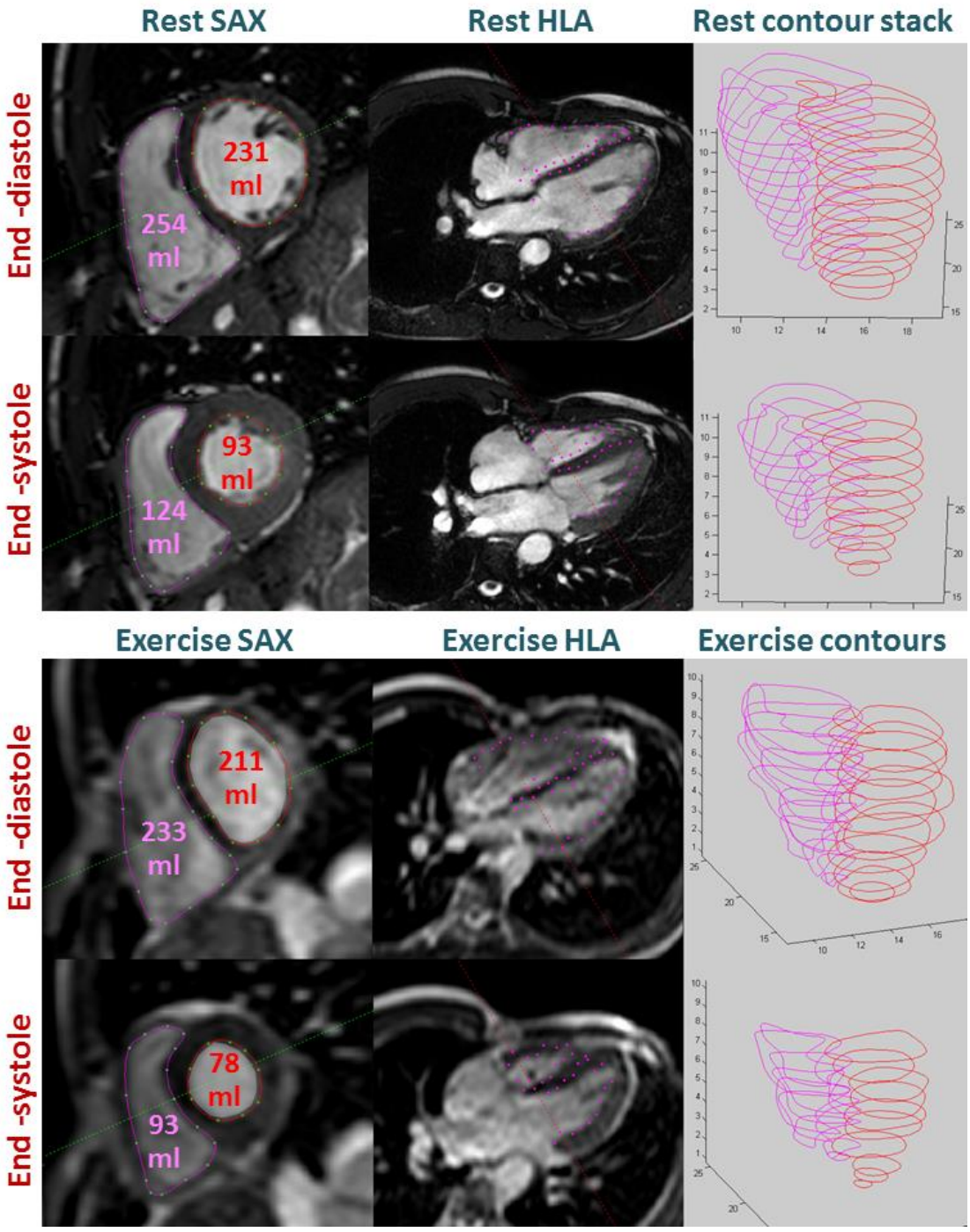


Figure 1-10 Example of real-time ungated CMR imaging at rest and during maximal exercise.

Ungated real-time biventricular volume assessment methodology as developed by La Gerche *et al* (198) and subsequently utilised in numerous clinical studies. Abbreviations: HLA, horizontal long axis, SAX, short axis.

It should be noted that the physiological response to exercise can differ depending on exercise type (aerobic/anaerobic/dynamic) and position (upright/semi-supine/supine) (222). Previous non-CMR exercise studies have published contradicting LVEDV responses to supine exercise, demonstrating an increase (259), a decrease (260) or no significant change (261-263) in LVEDV with exercise. However, a recent meta-analysis of LV function during supine Ex-CMR, involving a pooled analysis of 16 studies, demonstrated a significant rise in LVEF with exercise, driven by a fall in LVESV, whilst LVEDV remained unchanged (251).

1.2.4.4 In scanner flow assessment

Ex-CMR studies for flow assessment began by imaging during cessation of exercise and have progressed to free breathing acquisition during continuous exercise. Ex-CMR studies have predominantly assessed aortic and/or pulmonary artery flow, although flow assessment of the superior and inferior vena cava, left and right pulmonary arteries and all four pulmonary veins are feasible (264, 265). However, inferior vena cava flow assessment requires specialist sequences and respiratory compensation owing to significant diaphragmatic movement during exercise (265).

Initially Ex-CMR flow studies utilised retrospective cardiac gating with EPI sequences, with the initial study demonstrating feasibility at low resolution and heart rates equivalent of low exercise intensity (228). Faster imaging techniques were then adopted with EPI sequences and retrospective gating, reducing breath hold times to facilitate imaging after cessation of higher exercise intensities in healthy volunteers (236) and subsequently patients with congenital heart disease (81, 266).

Ex-CMR flow acquisition using retrospective cardiac gating with free breathing during exercise was first performed by Niezen *et al* in 1998 during low intensity exercise (229), and subsequently during moderate exercise intensity (237, 242) and post exercise cessation (264). Retrospective gating via pulse oximetry is commonly used to overcome ECG gating artefact at higher exercise intensities (229, 237).

To facilitate optimal image quality during free breathing continuous exercise, Ex-CMR studies assessing flow have utilised real time imaging. Various techniques have been developed, but require the use of either in-house plug-ins for open source software or in-house developed specialist software. Steeden *et al* used a spiral phase contrast real time sequence accelerated with sensitivity encoding (SENSE) to acquire aortic flow and a radial KT-SENSE sequence to assess LV volumes, during light/moderate exercise on the Lode BV (Up/Down) ergometer. Aortic flows acquired by the real time technique had good agreement at rest with a standard 2D retrospective free breathing flow acquisition technique and at rest and during exercise with the stroke volume from LV volumes (267). The same research group then utilised real-time unaliasing by Fourier-encoding the overlaps using the temporal dimension and sensitivity encoding spiral phase-contrast magnetic resonance sequence (UNFOLDed-SENSE) in subsequent studies. Initially the UNFOLDed-SENSE aortic flow sequence was used in a magnetic resonance augmented cardiopulmonary exercise test (MR-CPET) to demonstrated feasibility of MR-CPET in healthy adult volunteers (253) and subsequently in combination with real time k-t SENSE short axis cines to perform MR-CPET in paediatric healthy controls, repaired tetralogy of Fallot and pulmonary arterial hypertension (PAH) patients (254). A limitation of this continuous flow technique, highlighted by the authors, is the need to continuously measure flow to guarantee acquisition of data at peak exercise. This results in acquiring ≤25,000 frames of flow images and therefore creates a significant reconstruction and post processing problem. As such, the reconstruction requires an online graphics processing unit reconstruction system and in-house post processing tool to cope with the volume of data (254). Recently, ungated real time biventricular volume and aortic and pulmonary flows were performed during exercise to moderate exercise intensity in healthy volunteers and patients with pulmonary arterial hypertension, the flow volumes acquired were similar to stroke volumes acquired from biventricular volumes (268). Therefore, simultaneous Ex-CMR assessment of ventricular volumes and flow is feasible during continuous exercise and free breathing via either real-time or ‘un-gated real-time’ techniques, but all such techniques currently require the use of

specialist software/in-house software adaptation which may limit widespread attainability.

1.2.5 Upright cycle ergometer

Cheng *et al* demonstrated the feasibility of assessing pulmonary artery flow during continuous exercise to moderate intensity in adults and children in a 0.5T vertical open bore scanner (269). Although upright cycling may be more tolerated than supine exercise, it requires the use of an open low field MR scanner, with benefits of easing claustrophobia, but inherent issues of lower signal to noise ratio. CMR is feasible at lower field strengths (270), however, although the scanners are commercially available they are not in mainstream use, as such very few Ex-CMR studies have utilised this approach.

1.2.6 Isometric handgrip Ex-CMR

Isometric exercise involves the contraction of skeletal muscle without the elongation of the muscle, as such is also called static exercise (271). This is feasible during CMR by IHG exercise or isometric bicep exercise (272). IHG exercise comprises the constant squeezing of a lever on a hand dynamometer, generally to a percentage of the subjects maximum force. The technique only allows for modest increases in heart rate, typically 10-20bpm above resting rates, but causes minimal movement. As such, the technique has mainly been used for MR-spectroscopy (MRS) or coronary artery flow imaging where minimal movement artefact is pivotal and minimal HR increases are acceptable. Weiss *et al* performed the seminal work with IHG-Ex CMR, developing the phosphorus MRS (^{31}P-MRS) stress test which remarkably can detect ischaemia in patients with CAD, despite minimal stress and increases in heart rate (273).

1.2.7 Prone exercise CMR

Prone Ex-CMR was first employed by Conway *et al* who performed exercise MRS studies using knee extension with a custom system of straps, cables, pulleys and weights (274). Numerous subsequent Ex-CMR studies have similarly used prone Ex-CMR performing alternative knee flexion with ankle weights (275-277). Low-moderate intensity exercise is feasible by this approach, with the most significant response from the custom knee extension system by Conway *et al*, with a mean stress HR of 119bpm. This technique has other inherent limitations; exercising whilst prone is an unnatural form of exercise which uses weights or resistance bands attached to the legs, increasing the resistance can be labour intensive, requiring alterations during exercise/scanning or exercise cessation. Prone Ex-CMR often requires an auditory cue from a metronome to determine work speed, however if this isn't strictly adhered to, then the exact workload is unknown. As such, only Conway *et al* employed incremental resistance by increasing the attached weights to the pulley system used. As such, prone Ex-CMR is not ideal to assess incremental levels of exercise intensity or where strict HR increases or levels are required.

1.2.8 Exercise CMR assessment of cardiac disease

Ex-CMR has been utilised to study a wide range of cardiovascular pathology from coronary artery disease to potential cardiomyopathic conditions and structural/congenital heart disease. Ex-CMR is a larger field of research than appreciated, with over 70 publications using it as the primary investigative tool across a broad range of cardiac diseases. CAD has been investigated by treadmill Ex-CMR assessing regional wall motion and/or myocardial perfusion with post-stress imaging (197, 200, 202, 203, 211-213), or isometric handgrip exercise to assess coronary endothelial function by assessing coronary artery cross-sectional area change and coronary flow by velocity encoded CMR (278-281). Ex-CMR is developing as a useful tool in athletic heart disease with the ability to differentiate the athletic heart adaptation from cardiomyopathy, and to risk stratifying endurance athletes against RV arrhythmias (232, 234, 243). Of reassurance for the potential

widespread future application of Ex-CMR, even patients with complex congenital heart disease are able to perform supine exercise in the confines of the MR bore during Ex-CMR. Doing so, a wide range of congenital heart diseases have been investigated including: Fontan circulation (245, 246, 265, 266, 282, 283), transposition of the great arteries (81, 239, 248), tetralogy of Fallot (254, 284, 285) and ventricular septal defects (230). The numerous Ex-CMR studies in congenital heart disease is unsurprising given the unique ability of CMR to accurately image the right heart and complex congenital anatomies by allowing image acquisition in any plane. Ex-CMR studies in chronic pulmonary hypertension patients demonstrate reduced RV contractile reserve compared with healthy volunteers (233) and even those with iatrogenic induced acute pulmonary hypertension (268). Additionally, during Ex-CMR post pulmonary endartectomy CTEPH patients display an abnormal pulmonary vascular reserve, not appreciable via resting imaging, which can be partially reversed by Sildenafil (244). Ex-CMR studies demonstrate adolescent diabetics having decreased cardiac reserve compared with non-diabetic controls (249, 256, 257), which may be a result of impaired cardiac energetics being exacerbated by coronary microvascular dysfunction during exercise (277). Furthermore, multiple Ex-CMR studies have utilised ^{31}P-MRS as a non-invasive means of assessing the myocardial phosphocreatine to adenosine triphosphate concentration ratio, a sensitive indicator of myocardial energy status, to investigate multiple different cardiac diseases (273, 276, 277, 286-288).

1.2.8.1 Exercise CMR studies in valve disease

Despite the multiple Ex-CMR studies referenced in section 1.2.8 and the benefits CMR can offer in valve disease assessment, very few Ex-CMR studies have been performed in valve disease to date, with the small number of studies presented below.

Ex-CMR studies in aortic regurgitation (AR) have demonstrated that isolated AR in children and adults decreased during ‘steady state submaximal exercise’ CMR, which equated to prolonged light in-scanner exercise on a custom built device (289). Roberts *et al* assessed the short term effects metoprolol and losartan had on

exercise haemodynamics in chronic AR patients after supine exercise in a cross-over study, showing that with metoprolol there was a lower heart rate, greater AR regurgitant fraction, lower aortic distensibility and greater indexed EDV and ESV compared to Ex-CMR on losartan (290). Recently, a study by Chew *et al*, demonstrated the feasibility of assessing biventricular function during supine moderate intensity Ex-CMR in 5 primary MR patients, however simultaneous exercise PCMR aortic flow assessment was not performed, preventing quantification of MR during exercise, therefore further development and research is required to take full advantage of Ex-CMR in this patient cohort (93). An Ex-CMR study assessing the exercise biventricular response to percutaneous pulmonary valve implantation (PPVI) in patients with either PR or pulmonary stenosis of heterogeneous congenital aetiologies, demonstrated that PPVI resulted in restoration of RVEF exercise reserves in pulmonary stenosis patients but only a mild augmentation of exercise SV post PPVI in PR patients (291).

1.2.9 Comparing Ex-CMR methods

Within this section, all types of available/previously studied Ex-CMR methodologies have been presented, with each having benefits and weaknesses as displayed in Table 1-6. To date, treadmill Ex-CMR has demonstrated the most clinical utility, with the multicentre EXACT trial, demonstrating excellent diagnostic value in CAD and superiority over exercise MPS-SPECT (212). Additionally treadmill Ex-CMR is arguably the safest Ex-CMR technique to stress patients with suspected CAD, owing to exercise being performed with 12-lead ECG monitoring which is not feasible with in-scanner methods. Therefore currently, treadmill Ex-CMR is undoubtedly the first choice Ex-CMR method for diagnosing CAD and ischaemia assessment. Studies comparing treadmill Ex-CMR and pharmacological stress CMR, in the form of adenosine stress perfusion or dobutamine stress cine CMR have not been performed. Treadmill Ex-CMR also benefits from simultaneously performing a Bruce protocol treadmill test, which provides additional prognostic and diagnostic information. However as demonstrated in Figure 1-6, the average treadmill Ex-CMR test may take longer than pharmacological stress CMR and

requires additional specialist equipment and technician training. In-scanner Ex-CMR, as discussed, allows for CMR imaging during multiple stages of continuous exercise. As such, supine bicycle Ex-CMR is best placed for investigating biventricular response and/or flow changes in non-CAD. With further developments, the ability to perform biventricular volume, aortic and pulmonary flow assessment during exercise will allow for accurate direct quantification of aortic and pulmonary flow and indirect assessment of mitral and tricuspid regurgitation. Given resting CMR quantification of valvular regurgitant flow has demonstrated superior reproducibility and prognostic value over TTE (63, 64, 292) and an abnormal response during stress echocardiography can prompt intervention in asymptomatic valve disease (1), Ex-CMR could become an important clinical tool to assess valvular and congenital heart disease. However, commercially available MRI compatible supine cycle ergometers are expensive, therefore institutions wishing to perform Ex-CMR research, in which achieving maximal heart rates are not required, may opt to create a custom device or utilise cheaper alternatives such as prone exercise with ankle weights or resistance bands, indeed isometric hand grip may be preferable for performing exercise MRS as it produces minimal movement artefact and the modest HR increases achieved are sufficient to detect changes in numerous cardiac diseases.

1.2.10 Future of Ex-CMR

The potential clinical applications for Ex-CMR are considerable, however further technological developments and multicentre trials are needed to demonstrate the clinical utility of Ex-CMR. Ex-CMR will likely dichotomise into treadmill Ex-CMR as an investigation for CAD, and in-scanner Ex-CMR for non-CAD indications, owing to the safer monitoring treadmill Ex-CMR offers and the ability to assess biventricular volumes at numerous exercise stages with in-scanner Ex-CMR. The recently published multi-centre EXACT-COST trial may assist treadmill Ex-CMR gaining greater clinical use in CAD diagnosis and assessment (293). In-scanner Ex-CMR could benefit from new faster imaging techniques, to further reduce scanning and exercise time, to take full advantage of the multiparametric benefits

CMR offers. Development of imaging techniques which allow volume and flow assessment during continuous exercise that can be analysed in a timely fashion on commercially available software is another important need to increase attainability. The potential techniques to perform this include Compressed SENSE (C-SENSE) imaging with cine and PCMR sequences or the use of intracardiac 4D-flow.

1.2.10.1 Compressed SENSE

C-SENSE is a novel vendor provided parallel imaging technique that utilises both compressed sensing and SENSE parallel imaging to perform faster imaging. C-SENSE uses variable density subsampling combined with an iterative reconstruction algorithm thus combining the wavelet transformation of compressed sensing with the coil information of SENSE (294). By combing two fast imaging techniques it can be used to higher acceleration factors than SENSE alone (which is a clinical standard parallel imaging technique). As such C-SENSE acquires images faster than standard SENSE (295, 296). In addition, Compressed SENSE has been deemed more robust to respiratory motion than alternative parallel imaging techniques, as theoretically the iterative reconstruction process may reduce respiratory artefact (297) and studies demonstrate improved robustness to motion artefact than SENSE (298). Therefore at present, C-SENSE may theoretically be the optimal fast imaging technique for use with Ex-CMR, as it allows faster image acquisition (295), is robust to physical (298) and respiratory motion (297) and is now vendor provided, thus increasing widespread attainability. Research assessing the feasibility of using C-SENSE with Ex-CMR is therefore warranted.

1.2.10.2 4D-Flow

4D flow has recently emerged as a valuable research tool (299). Its use in Ex-CMR has recently been demonstrated as feasible during continuous supine stepper exercise in healthy volunteers by MacDonald *et al*. The study demonstrated excellent reproducibility of 4D flow in the ascending aorta and main pulmonary artery, but poor inter-observer reproducibility of quantified kinetic energy in the left and right ventricles (300). Clearly further research is needed with such emerging

techniques to further enhance the capabilities of Ex-CMR, but with further technological advances Ex-CMR could potentially revolutionise stress CMR.

1.2.11 Ex-CMR conclusion

Exercise CMR offers the potential to combine the superior imaging quality of CMR with the preferred and physiological method of stress by exercise. Numerous exercise options exist, including MRI scanner adjacent treadmills or in-scanner exercise with a supine cycle ergometer or stepper, prone exercise or isometric hand grip exercises. Imaging during maximal intensity in-scanner exercise is feasible using a supine cycle ergometer with ungated real-time imaging. Further advances are required to improve acquisition techniques and decrease scan time, to allow for a comprehensive multi-parametric assessment during exercise, which if feasible could revolutionise stress CMR.

1.3 Exercise prescription for cardiovascular imaging

Exercise prescription is the prescription of a defined exercise type and intensity to achieve a desired goal. In cardiac imaging the goal is often to ensure appropriate stress has been achieved and that it is done in a graduated manner to ensure safety, assess functional response and allow imaging at multiple exercise levels if required. Exercise imaging is an important aspect of this body of work. This section explains the methods in which to prescribe exercise intensity, determine maximal heart rates and assess the subjective and objective measures of exercise intensity. This understanding is vital to ensure exercise is individually prescribed to each patient to ensure equivalent stress levels are achieved despite differing resting variables and fitness levels between patients. Additionally, the general explanation that follows serves as a rationale for the methodology of the exercise prescription used in Chapters 2&3.

As described in Section 1.2, Ex-CMR has been utilised in multiple studies to various exercise intensities which differed depending on individual study aims. Exercise prescription is required with exercise cardiac imaging to define the level of stress required for the imaging indication. Exercise prescription requires determining the patients maximal exercise capacity to allow prescription of exercise levels as percentages of the maximal level. Maximal oxygen uptake (VO_{2max}) assessment during cardiopulmonary exercise testing (CPET) is the reference standard way to assess maximal exercise capacity/tolerance (301), therefore allowing intensities levels to be prescribed as a percentage of the confirmed individuals confirmed VO_{2max}. However, assessing heart rate response is often done in lieu of VO_{2max} as heart rate is easy to measure and increases in a linear fashion with VO_2 throughout exercise (302). As a result, for exercise cardiac imaging, patients response to exercise is commonly measured by assessing heart rate, usually to an age predicted maximal heart rate (HR_{max}), calculated using a formula, which is most often the 'HR_{max}=220-age' formula. The accuracy of the predicted maximal heart rate and resultant prescribed exercise stages is important to ensure patients are imaged at the desired intensity. Therefore, important

aspects pertaining to maximal heart rate prediction, exercise intensity prescription and subjective methods of assessing exercise intensity shall be discussed in the following sections.

1.3.1 Age predictive maximal heart rate formulas

As described the optimal method of assessing an individual's maximal exercise capacity is to derive VO_{2max} via CPET testing. However, for cardiovascular imaging, this would require an additional test, thus increasing the time and cost of exercise imaging. Therefore, age predictive maximal heart rate formulas are an accepted method to assist exercise prescription in lieu of performing CPET (201). Frequently utilised age predicted HR_{max} formulas are shown in Table 1-8. The commonest utilised equation clinically is 'HR_{max} = 220 –Age'. Although the use of this formula in stress echocardiography is advised by the ASE (83) and its simplicity has resulted in widespread use, the validity of the formula to accurately predict HR_{max} is surprisingly lacking (303). The original formula, attributed to Fox *et al* (304), was created as a rough formulation (with no regression analysis performed) of HR decline with age, from 10 studies with varying criteria for having reached HR_{max} ,with the majority investigated aged under 55 years old (303-305). Criticisms of this formula are that it can overestimate HR_{max} in younger patients and underestimate it in older patients (305-307). Thus, subsequent formulas, created via meta-analysis or laboratory testing, generally suggest a lower intercept and smaller age co-efficient (Table 1-8).

Numerous formulas have been created with varying demographics of the test group. Given predictive formulas should not be applied universally but ideally to the population in which they were tested (201), using a formula developed from a cohort with a wide age range, equal sex representation and broad range of physical fitness is important. One such formula was created by Tanaka *et al*: 'HRmax = 208 - (0.7 x age)'. The formula was initially developed from a meta-analysis of 18712 patients and then validated via laboratory testing on a further 514 patients (305). The meta-analysis involved 18712 patients from 351 studies, with the inclusion criteria of: English language studies, published in peer-reviewed

journals, at least 5 subjects per group, adult participants, data on men and women reported separately and the maximal exertion being documented using objective criteria. As the studies had varying groups of patients, in regards physical fitness, Tanaka *et al* allocated patients into one of three arbitrary groups: Endurance trained (regular vigorous endurance exercise ≥3 times a week for ≥1 year), active (occasional/ irregular aerobic exercise ≤2 times a week) or sedentary (no exercise). Treadmill and cycle ergometer data were pooled together as there was no significant difference between the two groups. The meta-analysis showed no significant difference in results between men and women for endurance trained (206 - 0.7 x age), active (207 - 0.7 x age) or sedentary groups (211 - 0.8 x age). When the groups are combined the formula created is: HRmax = 208 - (0.7 x age). A laboratory study was performed on 514 patients (277 women and 237 men) with a broad age range (18-81years). Patients with a body mass index (BMI) >35 were excluded. Maximal exertion was identified by ensuring patients had: a respiratory exchange ratio of ≥1.15, a plateau in VO_2 with increasing exercise, a respiratory rate (max) of ≥35 and a perceived rate of exertion of ≥18 on the Borg rating of perceived exertion (RPE) scale. The laboratory study formulated a regression equation of 'HR_{max} =(209 - 0.7xage)', which showed no significance difference between men or women and was not significantly different to the meta-analysis derived equation 'HR_{max} = (208 - 0.7xage)'. Therefore, 'HR_{max} = (208 - 0.7xage)' was advised as a more generalizable equation than 'HR_{max} = 220 –Age', but due to exclusion criteria, may not be valid in those with a BMI>35.

Table 1-8 Common equations for estimating maximal heart rate and the development method and study cohort

Equation	Author	Study method	Patient number	Population
220 – age	Fox *et al* (304)	Approximate fit from HR_{max} achieved in 10 studies	Not disclosed	Mostly <55yrs (304)
207 – (0.7 x age)	Gellish *et al* (308)	Longitudinal analysis of patients over a minimum of 6 annual GEX tests	132 (had a total of 908 GEX)*	100 men, 32 women, Age 27-78
206 – (0.88 x age)	Gulati *et al* (309)	ETT via Bruce protocol until symptoms or ECG changes (no VO_{2max} assessment)	5437 Women	Age 35-86
208 – (0.7 x age)	Tanaka *et al* (305)	Meta-analysis followed by CPET laboratory testing.	18712 (meta-analysis), 514 (study)	Study population: 237 men, 277 women, aged 18-81

Table 1-8 legend: * 132 participants had multiple GEX over several years, allowing assessment of results from 908 GEX. Abbreviations: CPET, cardio-pulmonary exercise test; ETT, exercise tolerance test; GEX, Graduated exercise test; HRmax, maximal heart rate; VO_{2max}, maximal oxygen uptake.

1.3.2 Prescribing exercise intensities

Once maximal exercise intensity has been discerned, prescription of the desired exercise intensity can be done as a percentage of the maximum. Estimating exercise intensity can be done via absolute or relative measures. Absolute measures include caloric expenditure, absolute oxygen uptake and metabolic equivalent tasks. However, absolute measures can misclassify exercise intensity as they do not take into account individual factors such as: age, body weight, sex and fitness level. Therefore relative methods are often preferred that include: percentage of HR_{max} (%HR_{max}), percentage of HR_{max} reserve method (%HRR), percentage of VO_{2max} (%VO_{2max}) and percentage of VO_2 reserve (%VO_2R) (201). Calculating the %HRR via the Karvonen method (310) involves calculating the difference between resting HR and maximal HR, dividing the value by the percentage of exercise intensity required and adding this value to the resting HR, as shown in Equation 8 (302, 310).

Equation 8 – How to calculate heart rate reserve percentage via Karvonen method

$$\%HRR = ((\mathrm{HRmax} - \mathrm{HR\ rest})\ \mathrm{x}\ \%\ \mathrm{desired\ intensity\ of\ exercise}) + \mathrm{HR\ rest}$$

%HRR and %VO_2R methods are often preferred for accurate exercise prescription over %HR_{max} and %VO_{2max} methods as these latter methods can under and overestimate exercise intensity in comparison (201, 311, 312). As such, numerous studies demonstrate that assessing rises in HR via the %HRR method correlates better with VO_{2max} than the %HR_{max} method (302, 313). This superior correlation has been attributed to the %HRR method taking into account resting heart rate and therefore the significant variations in resting heart rates than can occur between individuals. As such, %HRR is often preferred over %HR_{max} for exercise prescription (201). Indeed, as resting and exercise heart rates are lower in the supine than upright positions (227, 314), the use of the %HRR method is likely

preferable to a $\%HR_{max}$ method when prescribing exercise intensities for use during supine Ex-CMR as it should theoretically better account for this factor. The American College of Sports Medicine provide guidance on the classification of exercise intensity as presented in Table 1-9 (201).

Table 1-9 American college of sports medicine classifications of exercise intensity by relative methods.

Exercise Intensity	%HRR or $\%VO_2R$	$\%HR_{max}$	$\%VO_{2max}$	Borg scale RPE (6-20 scale)
Very light	<30	<57	<37	<9
Light	30-39	57-63	37-45	9-11
Moderate	40-59	64-76	46-63	12-13
Vigorous	60-89	77-95	64-90	14-17
Near maximal to maximal	≥ 90	≥ 96	≥ 91	≥ 18

Table 1-9 legend: Adapted from American College of Sports Medicine guidelines (201), Abbreviations: $\%HR_{max}$, percentage of maximal heart rate; %HRR, percentage of maximal heart rate reserve; RPE, rating of perceived exertion; $\%VO_{2max}$, percentage of maximum oxygen uptake; $\%VO_2R$, percentage of maximal oxygen uptake reserve.

1.3.3 Rate of perceived exertion

Another method to assess exercise intensity is by assessing the rate of perceived exertion (RPE), which can be a useful adjunct to assessing heart rate or oxygen uptake to assess both subjective and objective response to exercise. Borg *et al*, developed and refined the Borg scale for rating of perceived exertion (315), which correlates moderate-strongly with objective measures of exercise intensity (316, 317). An example of a Borg scale of ratings of perceive exertion is displayed in Table 1-10 and the classification of the points on this scale into exercise intensities is presented in Table 1-9.

Table 1-10 Rating of Perceived Exertion – Borg scale

Rating	Rating of Perceived Exertion
6	No Exertion
7	Extremely Light
8	
9	Very Light
10	
11	Light
12	
13	Somewhat hard
14	
15	Hard
16	
17	Very Hard
18	
19	Extremely Hard
20	Maximal exertion

1.4 Thesis aims/hypothesis

Mitral regurgitation is a common valve disease with multiple aetiologies and variables that effect prognosis and outcomes post-surgery/intervention. Primary mitral regurgitation can benefit from early intervention in carefully selected cases, to ensure preservation of LV function post-operatively. However, surgery is not without risk and therefore the accuracy of investigations advising intervention is paramount. TTE is the first line investigation in valvular heart disease (1, 39) and exercise-TTE provides additional prognostic information, not present at rest, to assist decision making (79, 80). However, as presented throughout this introductory chapter, CMR provides reference standard biventricular assessment (52, 53) and CMR quantified MR has superior reproducibility (59, 60, 62, 63) and prognostic ability compared to TTE (63, 64). Ex-CMR provides the ability to combine the superior image quality of CMR with the preferred method of stress. Therefore, further developments of Ex-CMR to allow biventricular function and MR quantification during exercise may provide a powerful tool to assist decision making in borderline cases of primary MR. To facilitate the widespread clinical use of Ex-CMR, protocols need developing using fast imaging techniques that can acquire high image quality using widely attainable sequences, software and equipment. C-SENSE has recently become vendor provided and offers fast image acquisition (295) and is robust to physical (298) and respiratory motion (297). As such C-SENSE may be well suited to use during Ex-CMR and warrants investigation.

Once the decision to intervene on mitral regurgitation has been made, patients deserve an optimal correction based upon evidence based medicine using the most accurate techniques to assess outcomes. Currently MVr, when feasible, is advised over MVR (1, 39). Although multiple comparative studies between MVr & MVR have been performed, there are several limitations that bias the comparison and no randomised studies have been performed in primary MR. The limitations of prior studies primarily revolve around: studies performed before the routine use of chordal preservation with MVR, the use of TTE to define MR severity and assess remodelling and the intrinsic bias that often exists between surgical groups with MVR groups often older with more comorbities. Many comparative studies predate

modern chordal preservation techniques with MVR (116-121) which when used demonstrate comparable cardiac reverse remodelling between MVr & MVR (126, 127). Given cardiac reverse remodelling is associated with a more favourable prognosis in a wide variety of cardiac diseases (128, 129), the lack of use in comparative studies is a significant limitation. Prior studies comparing outcomes between MVr/MVR have done so using TTE to define MR severity and therefore determine the need for surgery or assess cardiac remodelling using TTE. Given the inaccuracies and suboptimal reproducibility of MR assessment by TTE described in this introductory chapter, comparative studies may be biased by suboptimal patient selection. Finally, as described in section 1.1.4.2, patients referred for MVR are often older with more comorbidities (96), as such intrinsic bias often exist between prospective studies comparing MVr vs MVR. Given the greater risk of recurrent MR and potential for increased reoperations post MVr, updated studies comparing cardiac reverse remodelling and recurrent MR post MVr vs MVR with chordal preservation using the reference standard (CMR) are warranted. Ideally randomised trials comparing MVr vs MVR with chordal preservation using CMR, as the reference standard, to assess biventricular remodelling and quantify MR are warranted. However, due to the current evidence favouring MVr, rigorous hypothesis generating research is first required to ensure such studies are ethical and necessary. Additionally, the growing options of percutaneous treatments available to primary MR patients not suitable for surgery are increasing. Therefore continued research, accurately assessing outcomes is essential to assist optimal patient selection. Generally, smaller alterations in MR and cardiac reverse remodelling occurs post percutaneous intervention compared with surgical cohorts. As such, the increased accuracy offered by CMR is especially important when studying patients undergoing percutaneous intervention, to highlight smaller, but significant changes in MR and cardiac reverse remodelling and therefore assist in optimal future patient selection.

In this thesis the following studies have been performed, using CMR as the investigative tool, with the aims/hypothesis of each chapter as outlined:

Chapter 2) This study aimed to evaluate the feasibility and utility of biventricular function and flow assessment in healthy volunteers during continuous in-scanner exercise, using vendor supplied Compressed SENSE sequences and commercial analysis software.

Chapter 3) This study aimed to evaluate the feasibility and reproducibility of assessing biventricular volumes and MR quantification in primary MR patients during continuous supine Ex-CMR, using vendor provided image sequences and commercially available analysis software, and to describe the biventricular and quantitated MR changes during supine Ex-CMR in asymptomatic primary MR patients.

Chapter 4) This study aimed to assess the differences in cardiac reverse remodelling and MR reduction post MVr vs MVR with chordal preservation for significant primary MR, using sequential CMR and a longitudinal watchful-waiting control group (no surgical intervention) for comprehensive assessment.

Chapter 5) This study aimed to assess cardiac reverse remodelling and quantitate changes in valvular flow after percutaneous valve intervention for primary MR using the reference standard (CMR).

Each of the above chapters contain specific background, methods, results and discussion sections. Chapter 2 develops and validates the methodology subsequently utilised in chapter 3. Chapter 4 and 5 share similar methodology in separate cohorts of patients and are therefore presented separately. Chapter 6 provides an overall discussion with comparisons between the Ex-CMR results from Chapters 2 & 3 and comparisons of the cardiac reverse remodelling results from Chapters 4 & 5.

Chapter 2

Exercise cardiovascular magnetic resonance: feasibility of biventricular function and great vessel flow assessment during continuous exercise accelerated by Compressed SENSE

2.1 Abstract

Background

Exercise cardiovascular magnetic resonance (Ex-CMR) typically requires complex post-processing or transient exercise cessation, decreasing clinical utility. We aimed to demonstrate the feasibility of assessing biventricular volumes and great vessel flow during continuous in-scanner Ex-CMR, using vendor provided Compressed SENSE (C-SENSE) sequences and commercial analysis software (Cvi42).

Methods

12 healthy volunteers (8-male, age: 35±9years) underwent continuous supine cycle ergometer (Lode-BV) Ex-CMR (1.5T Philips, Ingenia). Free-breathing, respiratory navigated C-SENSE short-axis cines and aortic/pulmonary phase contrast magnetic resonance (PCMR) sequences were validated against clinical sequences at rest and used during low and moderate intensity Ex-CMR. Optimal PCMR C-SENSE acceleration, C-SENSE-3 (CS3) vs C-SENSE-6 (CS6), was further investigated by image quality scoring. Intra-and inter-operator reproducibility of biventricular and flow indices was performed.

Results

All CS3 PCMR image quality scores were superior ($p<0.05$) to CS6 sequences, except pulmonary PCMR at moderate exercise. Resting stroke volumes from clinical PCMR sequences showed stronger correlation with CS3 than CS6 sequences. Resting biventricular volumes from CS3 and clinical sequences correlated very strongly ($r>0.93$). During Ex-CMR, biventricular end-diastolic

volumes (EDV) remained unchanged, except right-ventricular EDV decreasing at moderate exercise. Biventricular ejection-fractions increased at each stage. Exercise biventricular cine and PCMR stroke volumes correlated very strongly ($r \geq 0.9$), demonstrating internal validity. Intra-observer reproducibility was excellent, co-efficient of variance (CV) <10%. Inter-observer reproducibility was excellent, except for resting right-ventricular and exercise bi-ventricular end-systolic volumes which were good (CV 10-20%).

Conclusion

Biventricular function, aortic and pulmonary flow assessment during continuous Ex-CMR using CS3 sequences is feasible, reproducible and analysable using commercially available software.

2.2 Introduction

Stress cardiac imaging is an important tool in assessing valvular (1) and congenital heart disease (194) and has significantly improved the diagnostic accuracy for CAD detection compared to exercise ECG (182, 183, 185). CMR has several well established benefits over alternative imaging modalities and as such is the current reference standard for bi-ventricular volume and functional assessment (52, 53). Pharmacological stress CMR is well established clinically and has demonstrated superiority over MPS-SPECT in the diagnosis (190, 318) and prognostication of CAD (191). However, physical exercise allows a more detailed assessment of symptoms, functional state and haemodynamic response to a graduated increase in workload and has fewer adverse events compared to pharmacological stress (80, 82). As such, current guidelines advise physical exercise as the preferred method for stress imaging when feasible (83, 84). Ex-CMR combines the superior image quality of CMR with the preferred method of stress by exercise. Despite development in research over the past 3 decades, Ex-CMR is not widely utilised clinically. Treadmill Ex-CMR has demonstrated clinical utility and superiority over MPS-SPECT, in the detection of ischaemia in CAD (212). However, heart rate reductions during transfer to the MRI-scanner limit its clinical utility beyond CAD assessment and make assessment at multiple exercise intensities logistically difficult. In-scanner Ex-CMR with a supine ergometer overcomes this issue, but CMR scanning during exercise results in increased physical movement, respiratory artefacts and ECG gating artefacts, all of which increase with increasing workload (198). Originally, Ex-CMR studies, using retrospective cardiac gating, performed imaging during exercise cessation and breath holding to overcome these issues (238), unfortunately both are non-physiological and reduce clinical utility. The development of un-gated real-time cine imaging, utilising post hoc cardiac and respiratory gating, has allowed biventricular volume assessment reliably to maximal exercise intensity (198). Recently, combining this technique with un-gated flow acquisition resulted in the first study assessing bi-ventricular volumes and aortic and pulmonary flow during continuous exercise (268). Unfortunately, the un-gated real-time technique requires specialist software (for post hoc cardiac and respiratory gating) and prolonged post processing and analysis time, thus

decreasing clinical utility and widespread attainability (198). Also, real time Ex-CMR studies assessing flow report the technique acquires a significant volume of flow data (<25000 images per patient), requiring the use of an online graphics processing unit reconstruction system (254). Therefore free-breathing methods that can acquire cine and flow image quality using retrospective cardiac gating during continuous exercise may increase the clinical utility of Ex-CMR, as specialist software and sequences will not be required. Thus increasing attainability and reducing post-processing/analysis time. Indeed recently, biventricular volume assessment during free breathing continuous exercise using retrospective cardiac gating was proven feasible, by using SENSE-2 short axis cine sequences with respiratory navigation to compensate for respiratory motion, the use of retrospective cardiac gating in this study allowed analysis on standard commercially available software (93). Given the ability to assess biventricular haemodynamic response and flow through the aortic and pulmonary valves during exercise could allow accurate assessment and quantification of valvular heart disease and congenital heart disease, a clinically attainable protocol assessing both volumes and flow is inviting. However, faster imaging is required to acquire PCMR sequences in addition to cine imaging during Ex-CMR before the onset of leg fatigue. As highlighted in section 1.2.10.1, C-SENSE is a novel vendor provided parallel imaging technique. By combining compressed sensing and SENSE parallel imaging, higher acceleration factors and thus faster imaging can be performed than by using SENSE alone (295, 296). C-SENSE is reportedly more robust to physical (298) and respiratory motion (297) than alternative parallel imaging techniques. Therefore C-SENSE sequences may be the optimal technique to facilitate biventricular function and flow assessment using retrospective cardiac gating. To date, C-SENSE has not previously been utilised in Ex-CMR. This study aimed to demonstrate the feasibility of assessing biventricular volume and flow during continuous exercise using vendor provided C-SENSE sequences and commercially available standard analysis software.

2.3 Methods

2.3.1 Study design

Protocol development and feasibility testing was achieved by: 1) developing a free-breathing C-SENSE protocol and validating this against our institute's standard clinical imaging sequences at rest; 2) determining the optimal acceleration of C-SENSE for PCMR sequences, for use in Ex-CMR, by assessing resting and exercise image quality and comparing the derived stroke volumes against standard clinical imaging sequences at rest; 3) utilising the C-SENSE protocol (validated against clinical sequences at rest) during continuous low and moderate exercise intensities to determine if the acquired biventricular volumes and flow have internal validity in terms of consistency of ventricular stroke volumes when derived separately from cavity volumes and great vessel flow measurements, and whether they are concordant with expected supine exercise physiology.

A supine cycle ergometer (Lode BV) Ex-CMR was preferred to alternative stress modalities due to the ability to perform in-scanner imaging during exercise to reasonable exercise intensities as compared with alternative modalities discussed in Chapter 1.2. C-SENSE was chosen due to its faster image acquisition and increased robustness to respiratory and physical motion than other parallel imaging techniques as discussed in section 1.2.10.1 (295-298). Retrospective cardiac gating was utilised in this study because, as described in Chapter 1.2, it does not require specialist sequences or software and thus ensures our developed technique has increased widespread attainability and potentially reduced post-processing/analysis time compared with real-time/ungated techniques.

This study was approved by a local ethics committee in England (Yorkshire and the Humber – Leeds East **18/YH/0168)**. All participants provided written informed consent. All Ex-CMR studies were performed at the Leeds General Infirmary, UK (See appendix).

2.3.2 Study population

12 healthy volunteers (8 male, 4 female), aged 35±9 years (mean±standard deviation) (range 23-56 years) underwent CMR at rest and during continuous exercise using the Lode BV supine bicycle ergometer. Participants were of a healthy weight (BMI 23.9±2.3) and of varying levels of physical fitness, performing regular exercise between 0.5 and 15 hours a week (mean 5.0±3.5hours). All healthy volunteers had no significant co-morbidities and no contraindications to exercise testing as per AHA guidelines (222).

2.3.3 Patient preparation

Specific patient preparations were undertaken to reduce common issues encountered in supine Ex-CMR, namely motion, respiratory and cardiac gating artefacts, to ensure optimal image quality. Prior to entering the scanner room patients were counselled on the importance keeping upper body movement to a minimum, this was facilitated by ensuring patients held onto the handles attached to the ergometer to help steady their upper body (Figure 2-1b). The patient's feet were securely strapped to the pedals of the cycle ergometer, with additional straps applied around the feet, if required, to ensure a secure fit, thus smoother cycling and reduced excessive motion. Prior Ex-CMR studies report that cycling movement can be restricted by leg contact with the MR bore (93). Therefore, prior to scan initiation, patient position was optimised, with a trial in the MR bore whilst attached to the cycle ergometer, to ensure cycling could be comfortably performed without the knee contacting the MR bore and patients advised against moving from this position during Ex-CMR. To reduce ECG/cardiac gating artefact, prior to ECG placement, the patient's chest was optimally prepared, including shaving where required and cleaning of the skin surface, the ECG was then secured to the patient's chest with tape to reduce movement. The receiver coil was placed on the patient atop padding placed at the patient's sides to reduce/remove contact between the coil and ECG leads during exercise which may produce ECG artefact. Pad positioning was individually optimised for each patient to ensure receiver coil placement did not cover the face or restrict cycling movement. Straps were placed around the patient and receiver coil to reduce motion artefact (Figure 2-1).

2.3.4 Exercise protocol

Participants performed supine cycle ergometer (Lode BV, Netherlands) (Figure 2-1) exercise during CMR using heart rate reserve and an age predictive maximal heart rate model (305), to prescribe individualised low (30-39% HRR) and moderate (40-59% HRR) exercise intensities. As described in Chapter 1.3, age-predictive HR models are an acceptable substitute for CPET defined maximal HR, when necessary (201). The use of prior CPET to define maximal HR was purposefully avoided in this study to remove an additional step in any resultant developed Ex-CMR protocol. The age-predictive maximal HR formula validated by Tanaka *et al* (HR_{max} = 208 - 0.7 x age) was used due to its rigorous validation in a generalizable population, as described in Chapter 1.3.1 (305). The %HRR/Karvonen method was used to prescribe exercise intensities from the calculated HR_{max} as it better accounts for lower resting and exercising HR in the supine position (201).

After completion of resting imaging, participants exercised with no resistance, 0 Watts (W), for 1 minute at a cycling cadence of 60-70rpm (with verbal feedback given to maintain this) then at an increase of 25W every 2 minutes until ‘low intensity’ target heart rate (THR) was achieved; once THR was achieved, smaller alterations in resistance wattage were made to maintain THR. HR was stabilised for 30 seconds prior to initiating imaging. After completion of imaging at low exercise intensity, resistance was increased by 25W initially and every 2 minutes until the prescribed moderate intensity was reached and HR stabilised for 30 seconds prior to initiating imaging. Exercise performed was continuous and all exercise imaging acquired during free-breathing. Participants perceived rate of exertion were assessed on the Borg scale (Table 1-10) after exercise cessation, to ensure correlation with prescribed intensity CMR imaging.

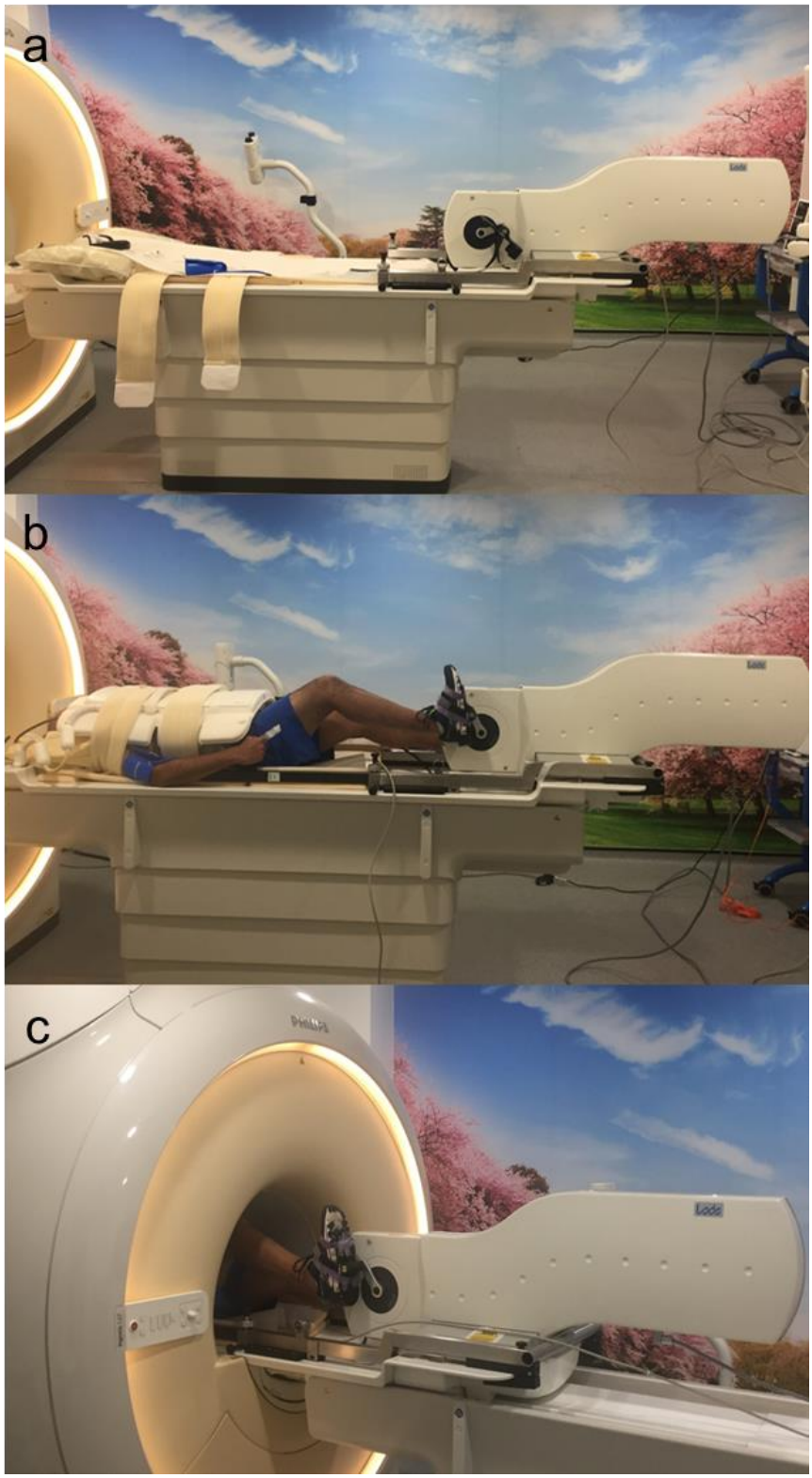


Figure 2-1 The Lode BV supine cycle ergometer

Supine cycle ergometer before (a), during set up (b) and during use (c).

2.3.5 CMR imaging

CMR imaging was performed on a dedicated cardiovascular 1.5 Tesla MRI system (Philips Ingenia system, Best, Netherlands). Initial survey and cine imaging was performed including: vertical long axis, horizontal long axis, LVOT and right ventricular outflow tract (RVOT) views. At rest, our institute's standard clinical protocol to assess biventricular volumes, aortic and pulmonary flow was performed to validate the novel C-SENSE protocol. The C-SENSE protocol was used at rest and during continuous exercise to low and moderate intensities. All image acquisitions, including cine imaging and PCMR imaging, were retrospectively cardiac gated. Through-plane velocity encoded (VENC) PCMR was acquired at the aortic sino-tubular junction for aortic PCMR and in the main pulmonary artery (MPA) 1cm superior to the valve for pulmonary PCMR. Resting VENC was set to 150 cm/s and increased to 250cm/s during exercise; the VENC was increased further if aliasing occurred. All PCMR sequences were planned with region of interest in the iso-centre of the MRI scanner to reduce background phase-offset errors (74, 75).

2.3.5.1 Standard clinical protocol

At rest, our institute's standard clinical protocol was performed, to allow validation of the novel C-SENSE protocol. Biventricular function was assessed using a breath-hold multi-phase, multi-slice short axis cine imaging stack. Great vessel flow was assessed from aortic and pulmonary through-plane phase contrast velocity mapping acquired during breath-hold (SENSE 2) and a separate free-breathing acquisition (no parallel imaging) to ensure a comprehensive comparison with the novel C-SENSE protocol.

The clinical short axis cine imaging parameters were as follows: typical field of view (FOV) 360x300mm, repetition time (TR) 3.1msec, echo time (TE) 1.56msec, flip angle 60°, SENSE factor 2, multishot turbo field echo (TFE) factor 12, TFE acquisition duration 37.4ms, phase percentage 67%, slice thickness 10mm, 0mm gap, 30 phases, in-plane spatial resolution acquired at 1.88×1.88mm and

reconstructed to 1.25x.125mm, matrix 192x158, planned acquisition involved 7x 8-second breath-holds.

The Clinical breath held (SENSE 2) PCMR sequence imaging parameters were: typical FOV 350x320mm, TR 4.9msec, TE 2.9msec, flip angle 15°, number of signal averages 1, TFE factor 4, slice thickness 8mm, 30 phases, phase percentage 67%, acquired in-plane spatial resolution 2.5×2.5mm reconstructed to 1.22x1.22mm, matrix 140x128, Cartesian sampling, planned acquisition time 13 seconds.

The Clinical free-breathing sequence (with no parallel imaging) imaging parameters were: typical FOV 400x280mm, TR 17msec, TE 2.4msec, flip angle 40°, number of signal averages 1, slice thickness 6mm, 40 phases, in-plane spatial resolution 1.56×2.23mm, matrix 256x126, Cartesian sampling, typical acquisition duration: 101 seconds.

2.3.5.2 C-SENSE protocol

The evaluation protocol involved biventricular function assessment by free-breathing, respiratory navigated, continuous cine imaging in short axis geometry accelerated by a C-SENSE factor of 3 (CS3). Great vessel flow was assessed by aortic and pulmonary through-plane phase-contrast imaging, with two separate free-breathing acquisitions using CS3 and C-SENSE 6 (CS6) acceleration. CS3 and CS6 flow acquisitions were acquired to investigate if a higher acceleration would result in better image quality as a faster acquisition may be less prone to respiratory artefact.

The C-SENSE short axis cine imaging parameters were as follows: typical FOV 300x300mm, TR 2.4msec, TE 1.21msec, flip angle 60°, temporal resolution 32msec. C-SENSE factor 3, multishot TFE factor 13, TFE acquisition duration 31.5ms, phase percentage 67%, slice thickness 10mm, 0mm gap, in-plane spatial resolution acquired at 2.5×2.5mm and reconstructed to 1.34x1.34mm, matrix 120x120, planned acquisition time 39 seconds. Respiratory navigation was used with the respiratory echo-based navigator positioned on the right hemi-diaphragm using a 5mm acceptance window with continuous gating level drift.

Imaging parameters of the CS3 and CS6 gradient echo PCMR sequences were: typical FOV 350x320mm, TR 4.9msec, TE 2.9msec, flip angle 15°, number of signal averages 1, TFE factor 4, slice thickness 8mm, 30 phases, phase percentage 67%, acquired in-plane spatial resolution 2.5×2.5mm reconstructed to 1.22x1.22mm, matrix 140x128, Cartesian sampling, planned acquisition time (per slice) of 9 and 5 seconds for CS3 and CS6 PCMR sequences respectively. To accommodate for potential through-plane motion during exercise, the CS3 and CS6 PCMR sequences were performed using a novel ‘PCMR-imaging stack’ acquiring 3x8mm overlapping PC-slices orthogonal to vessel flow (Figure 2-2). Aortic PCMR sequences used a -3mm gap (thus the centre of the slices are spaced 5mm apart) and the pulmonary flows had -5mm gap (thus the centre of the slices are spaced 3mm apart).The increased overlap of the pulmonary PCMR sequences was to accommodate for the short length of the main pulmonary artery prior to bifurcation, which has led to difficulty performing pulmonary PCMR in previous Ex-CMR studies (224).

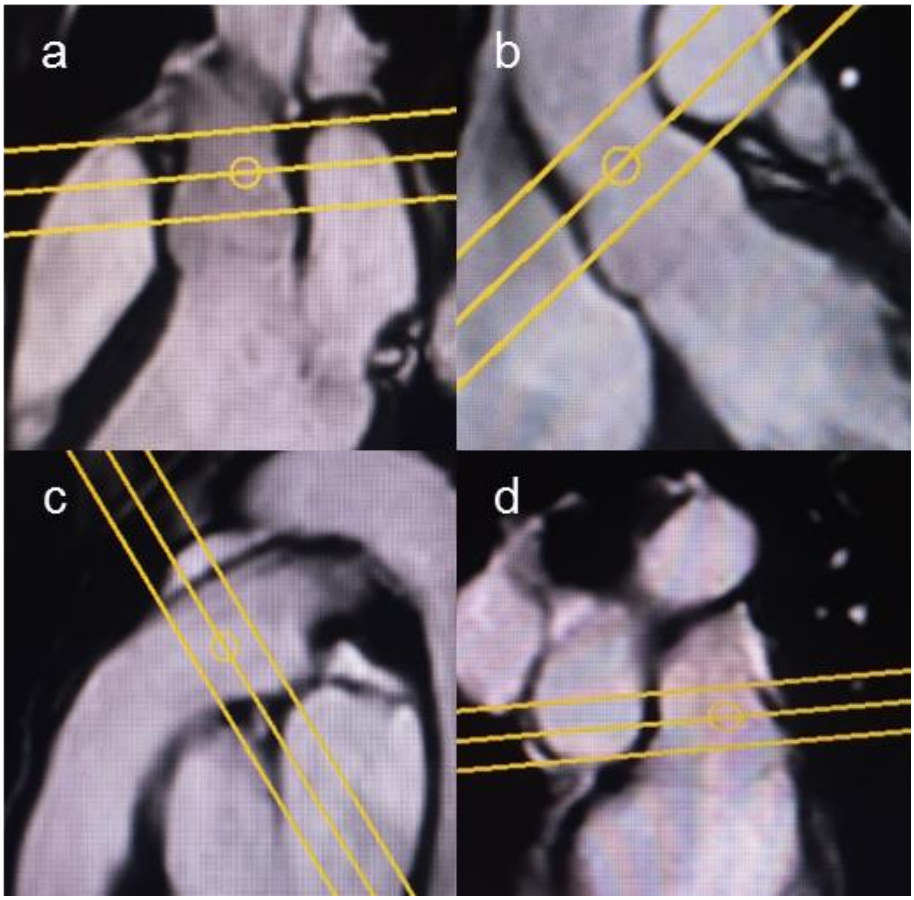


Figure 2-2 Novel phase contrast magnetic resonance (PCMR) stack technique

Example of planning of an aortic (A&B) and pulmonary (C&D) PCMR-stack. Aortic PCMR-stack geometry, 8mm slices with -3mm slice gap. Pulmonary PCMR-stack geometry, 8mm slices with -5mm slice gap. A) planning of aortic PCMR-stack in LVOT1 geometry. B) planning of aortic PCMR-stack in LVOT2 geometry. C) planning of pulmonary PCMR-stack in RVOT1 geometry. D) planning of pulmonary PCMR-stack in RVOT2 geometry. Abbreviations: LVOT, left ventricular outflow tract; PCMR, phase contrast magnetic resonance; RVOT, right ventricular outflow tract.

2.3.5.3 CMR imaging during exercise

During exercise, the above evaluation C-SENSE protocol was used with the addition of free-breathing 4-chamber and LVOT/RVOT cine imaging being performed to assess for movement during exercise and re-plan the short-axis cine imaging and phase contrast imaging geometry if required.

2.3.5.4 CMR analysis

Images were analysed using commercially available software (cvi42, Circle Cardiovascular Imaging, Calgary, AB, Canada). LV and RV endocardial contours were manually traced with the papillary muscles and trabeculations considered part of the ventricular blood pool and volumes calculated by summation of disks (319). Aortic and pulmonary flows were assessed by manually contouring the vessel endovascular contour in every phase. The CS3/CS6 PCMR-stack was assessed for the slice closest resembling the resting standard clinical acquisition to ensure all PCMR images had flow assessed at the same anatomical level. Image quality assessment was performed on all assessed PCMR images independently by two assessors (TC & NJ), whom were blinded to each-others results. Image quality was graded on the following scale: 3- excellent, 2- good, 1- adequate & 0- non diagnostic; the mean image quality scores from both assessors are presented.

2.3.6 Statistical analysis

Data were analysed using SPSS version 26 (IBM Corp.) and Microsoft Excel 2010. All continuous data were assessed for normality using Shapiro-Wilk test. Resting biventricular parameters comparing the breath-held standard clinical with CS3 respiratory navigated SA acquisitions were assessed by Pearsons correlation and the bias and limits of agreement by Bland-Altman plots. PCMR image quality scores were assessed by Wilcoxon signed ranks test and the stroke volume comparisons assessed by repeated measures analysis of variance (ANOVA) with Bonferroni post-test analysis. Repeated measures ANOVA with Bonferroni post-test analysis was used to compare cardiac volumetric and flow data between rest and different stages of exercise. Intra-observer analysis was performed by TC and inter-observer analysis by NJ; reproducibility was assessed by the Coefficient of Variation (CV) test, the standard deviation of differences between observations divided by the mean and by intra-class correlation (ICC) with a two way random model for absolute agreement. $P<0.05$ was considered statistically significant. Intra and inter-observer analysis was performed in a blinded method.

2.4 Results

13 healthy volunteers completed the study protocol, 1 volunteer was excluded due to ECG gating issues at moderate exercise intensity, leaving 12 healthy volunteers for analysis (8 male, age 35±9 years, BMI 23.9±2.3 kg/m^2).

2.4.1 Validation of Compressed SENSE protocol at rest

The novel C-SENSE protocol was validated against clinical standard sequences at rest, before being used during Ex-CMR.

2.4.1.1 Biventricular assessment

At rest, there were no significant differences between the biventricular volumes assessed by the standard clinical or novel CS3 short axis sequences, with all parameters demonstrating and very strong correlation ($r > 0.93$, $p < 0.01$) (Table 2-1), minimal bias and acceptable limits of agreement of left ventricular (Figure 2-4) and right ventricular (Figure 2-5) indices. Figure 2-3 demonstrates the typical image quality comparison between the resting breath-hold standard clinical and free-breathing CS3 short axis sequences.

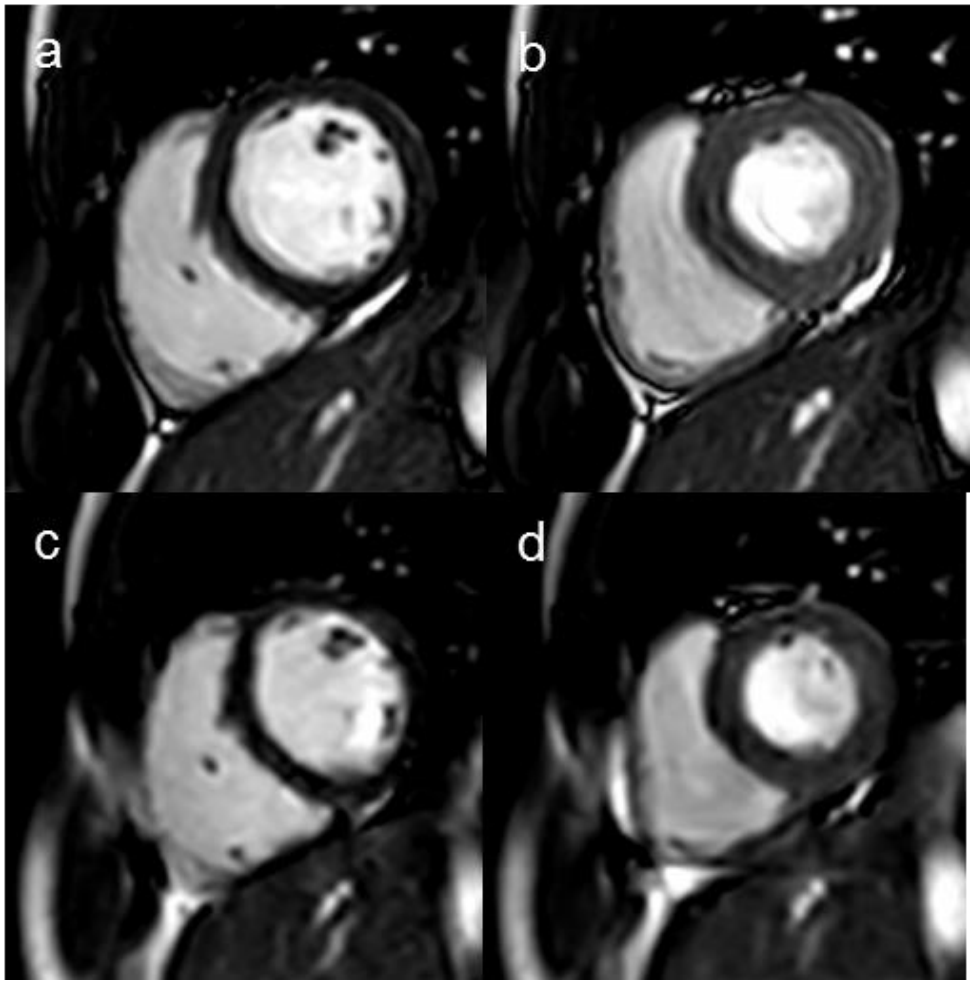


Figure 2-3 Comparison of resting short axis cine image quality acquired by clinical breath held SENSE 2 sequences and Compressed SENSE 3 respiratory navigated sequences

Clinical breath held SENSE 2 sequences at end-diastole (a) and end-systole (b) and Compressed SENSE 3 respiratory navigated sequences at and end-diastole (c) and end-systole (d).

Table 2-1 Validation of Compressed SENSE 3 free-breathing short axis cine sequences at rest vs breath-held clinical standard

Measurement	Image Sequence		Bland Altman				Correlation coefficient	
	Clinical	CS3	RC	Upper	Lower	Bias	R	p-value
LVEDV (ml)	165±39	164±39	7.05	6.34	-7.76	-0.71	0.996	<0.01
LVEDVi (ml/m^2)	88.8±16	88.5±16	3.69	3.33	-4.05	-0.36	0.994	<0.01
LVESV (ml)	73±23	71±23	10.38	9.46	-11.29	-0.92	0.976	<0.01
LVESVi (ml/m^2)	38.9±10	38.4±11	5.42	4.95	-5.88	-0.46	0.971	<0.01
LVSV (ml)	92±19	93±19	6.38	6.58	-6.18	0.2	0.986	<0.01
LVSVi (ml/m^2)	50±7	50±7	3.35	3.46	-3.24	0.11	0.974	<0.01
LVEF (%)	57±6	57±6	4.74	5.2	-4.28	0.46	0.932	<0.01
RVEDV (ml)	166±36	166±34	8.59	9.21	-7.96	0.62	0.995	<0.01
RVEDVi (ml/m^2)	89.4±16	89.8±15	4.74	5.15	-4.34	0.41	0.991	<0.01
RVESV (ml)	75±24	75±21	7.27	6.78	-7.76	-0.49	0.992	<0.01
RVESVi (ml/m^2)	40.6±11	40.4±10	3.84	3.6	-4.07	-0.23	0.99	<0.01
RVSV (ml)	90±18	91±17	6.46	7.56	-5.35	1.1	0.985	<0.01
RVSVi (ml/m^2)	48.8±8	49.4±7	3.51	4.15	-2.88	0.63	0.977	<0.01
RVEF (%)	55±7	56±6	2.82	3.23	-2.42	0.4	0.985	<0.01

Abbreviations: CS3, Compressed SENSE 3; EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; HR, heart rate; i, Indexed to body surface area; LV, left ventricle; RC, repeatability coefficient; RV, right ventricle; SV, stroke volume.

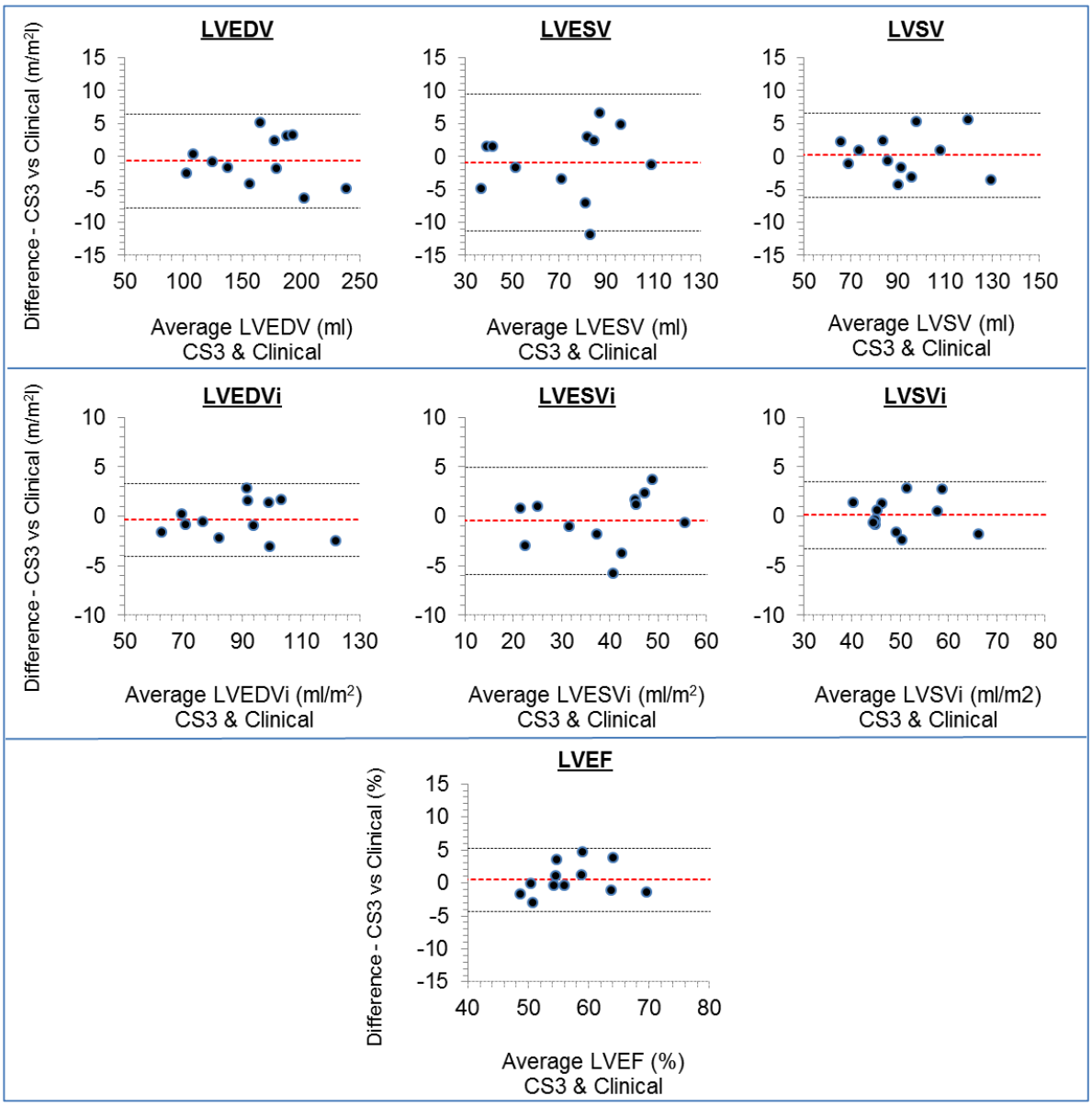


Figure 2-4 Bland Altman plots comparing left ventricular indices derived from Compressed SENSE 3 vs clinical short axis cine sequences

Dashed red line represents mean bias (mean difference in cardiac parameter between the CS3 and clinical sequences). Dashed black lines represent the 95% limits of agreement. Abbreviations: CS3, Compressed SENSE 3; EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; i, Indexed to body surface area; LV, left ventricle; SV, stroke volume.

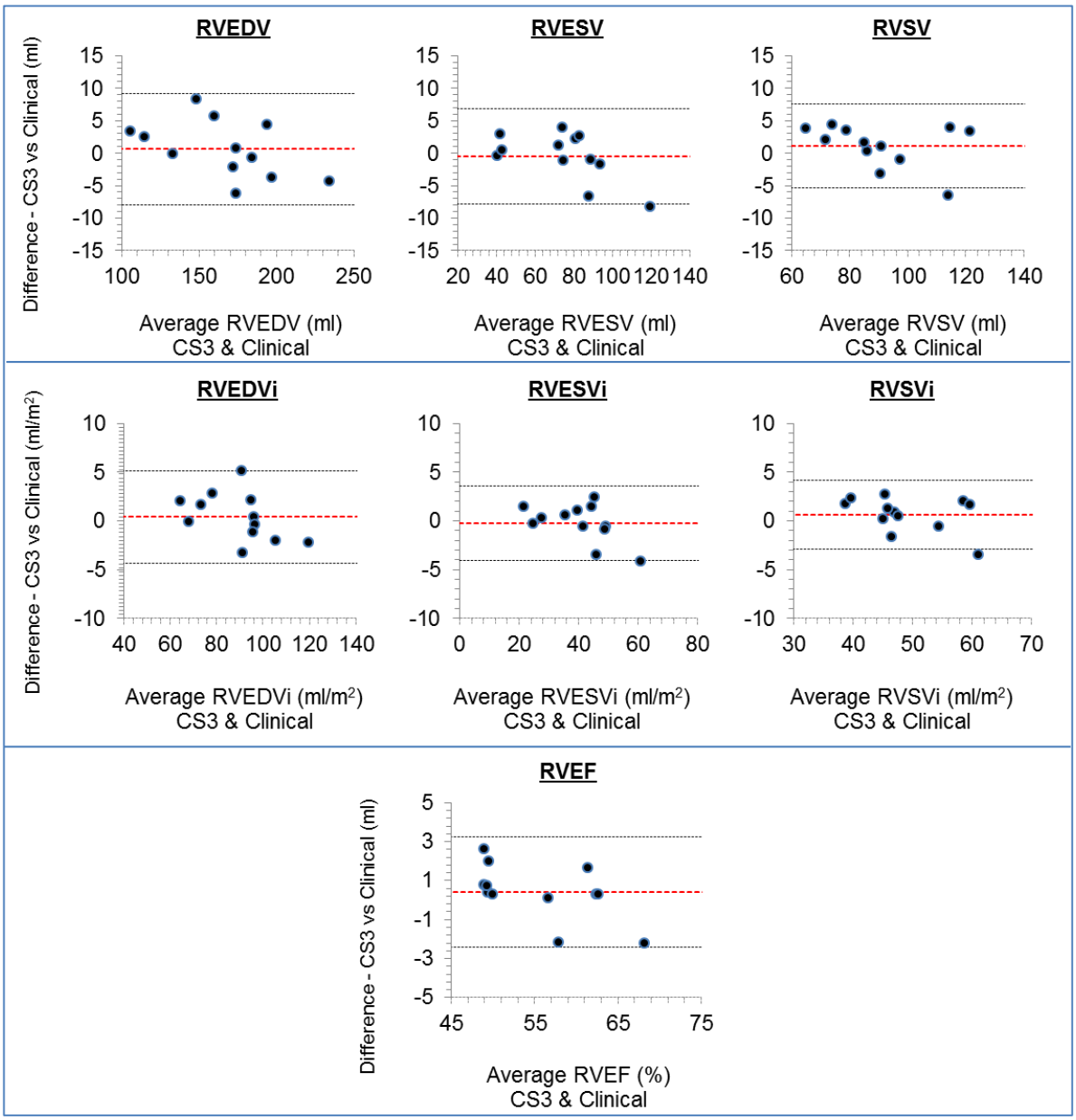


Figure 2-5 Bland Altman plots comparing right ventricular indices derived from Compressed SENSE 3 vs clinical short axis cine sequences

Dashed red line represents mean bias (mean difference in cardiac parameter between the CS3 and clinical sequences). Dashed black lines represent the 95% limits of agreement. Abbreviations: CS3, Compressed SENSE 3; EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; i, Indexed to body surface area; RV, right ventricle; SV, stroke volume.

2.4.1.2 Comparison of resting PCMR sequences

Mean resting aortic and pulmonary stroke volumes acquired from all 4 PCMR sequences were comparable, with CS3 and CS6 free-breathing flow showing minimal bias with both breath-hold and free-breathing standard clinical flow sequences (Table 2-2). Bias and limits of agreement of attained indexed stroke volumes from different PCMR sequences were assessed by Bland Altman plots for aortic (Figure 2-6) and pulmonary flow (Figure 2-7). When compared with the current clinical standard breath held imaging, CS3 sequences showed minimal bias (aortic flow -0.12m/m^{2-}, pulmonary flow -0.69ml/m^2) and acceptable limits of agreement for aortic (upper limit 3.98ml/m^2, lower limit -4.23ml/m^2) and pulmonary flow (upper limit 5.9ml/m^2, lower limit -7.29ml/m^2). Whilst in comparison with clinical breath held sequences, CS6 sequences showed minimally greater bias (aortic flow -2.15m/m^{2-}, pulmonary flow -0.73ml/m^2) and wider limits of agreement for aortic (upper limit 5.61 ml/m^2, lower limit -9.91ml/m^2) and pulmonary flow (upper limit 6.37ml/m^2, lower limit -7.82ml/m^2). CS6 aortic flow measurements were more prone to underestimate aortic flow, with a bias of -2.15ml/m^2/cardiac cycle against the breath-hold clinical standard in comparison to a minimal bias of -0.12 ml/m^2/cardiac cycle using a CS3 flow sequence. Additionally, pulmonary stroke volumes from CS6 sequences only demonstrated moderate correlation with clinical free-breathing sequences (r=0.655). Therefore, compared with CS6 sequences, CS3 sequences show less bias, stricter limits of agreement and stronger correlation with clinical breath held sequences and pulmonary free breathing sequences. As such, results demonstrate CS3 sequences to closer represent the clinical standard than CS6 sequences, with minimal significant difference in aortic or pulmonary flow assessment compared with clinical standard sequences.

Table 2-2 Summary of comparisons of resting indexed stroke volumes derived from clinical and C-SENSE accelerated aortic and pulmonary flow sequences by Bland Altman plots and Pearson correlation coefficient

Vessel & Sequence		SV (ml/m^2)	Flow comparison Vs Clinical BH					Flow comparison Vs Clinical FB				
			Bland Altman				Correlation Coefficient	Bland Altman				Correlation Coefficient
			RC	Limits of agreement		Bias (ml/m^2)		RC	Limits of agreement		Bias (ml/m^2)	
				Upper	Lower		r-value		Upper	Lower		r-value
Aorta	BH	48.3±7.1						9.49	9.6	-9.38	0.11	0.762
	FB	48.4±5.7	9.49	9.6	-9.38	-0.11	0.762					
	CS3	48.2±6.7	4.1	3.98	-4.23	-0.12	0.96	6.83	6.6	-7.06	-0.23	0.865
	CS6	46.2±6.4	7.76	5.61	-9.91	-2.15	0.849	6.38	4.12	-8.64	-2.26	0.873
Pulmonary	BH	48.9±5.9						8.01	7.48	-8.54	0.53	0.8
	FB	48.3±6.4	8.01	7.48	-8.54	-0.53	0.8					
	CS3	48.2±7.6	6.6	5.91	-7.29	-0.69	0.915	11	6.39	-6.71	-0.16	0.909
	CS6	48.1±6.6	7.1	6.37	-7.82	-0.73	0.85	6.55	10.8	-11.2	-0.2	0.655

Abbreviations: BH, breath hold; CS3/CS6, compressed SENSE 3/6; FB, free-breathing; SV, stroke volume

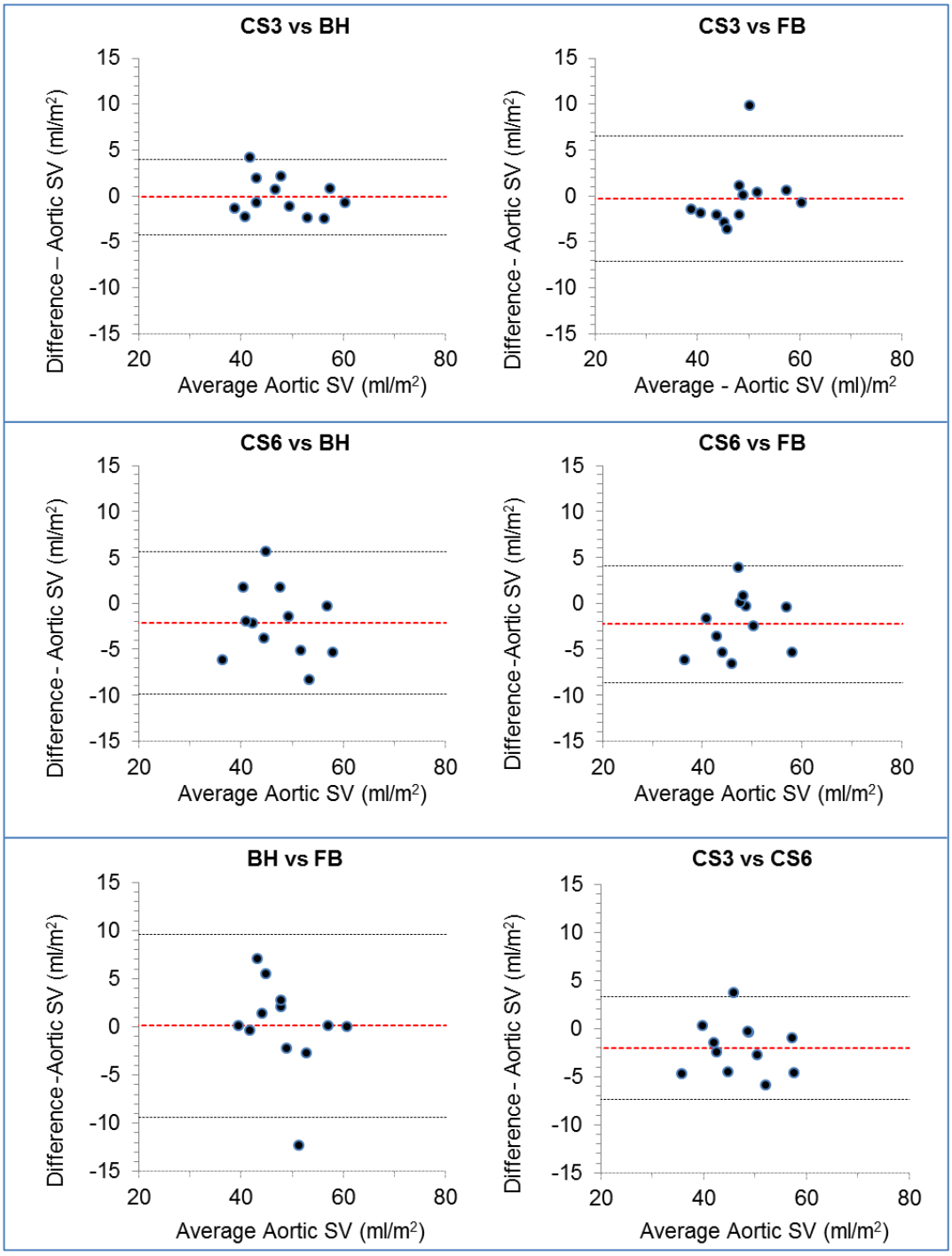


Figure 2-6 Bland Altman plots comparing resting indexed aortic stroke volumes Dashed red line represents mean bias (mean difference in cardiac parameter between the CS3 and clinical sequences). Dashed black lines represent the 95% limits of agreement. Aortic stroke volumes (SV) (ml/m^2/cardiac cycle) derived from breath held (BH), free breathing (FB), Compressed SENSE 3 (CS3) and Compressed SENSE 6 (CS6) aortic phase contrast magnetic resonance sequences.

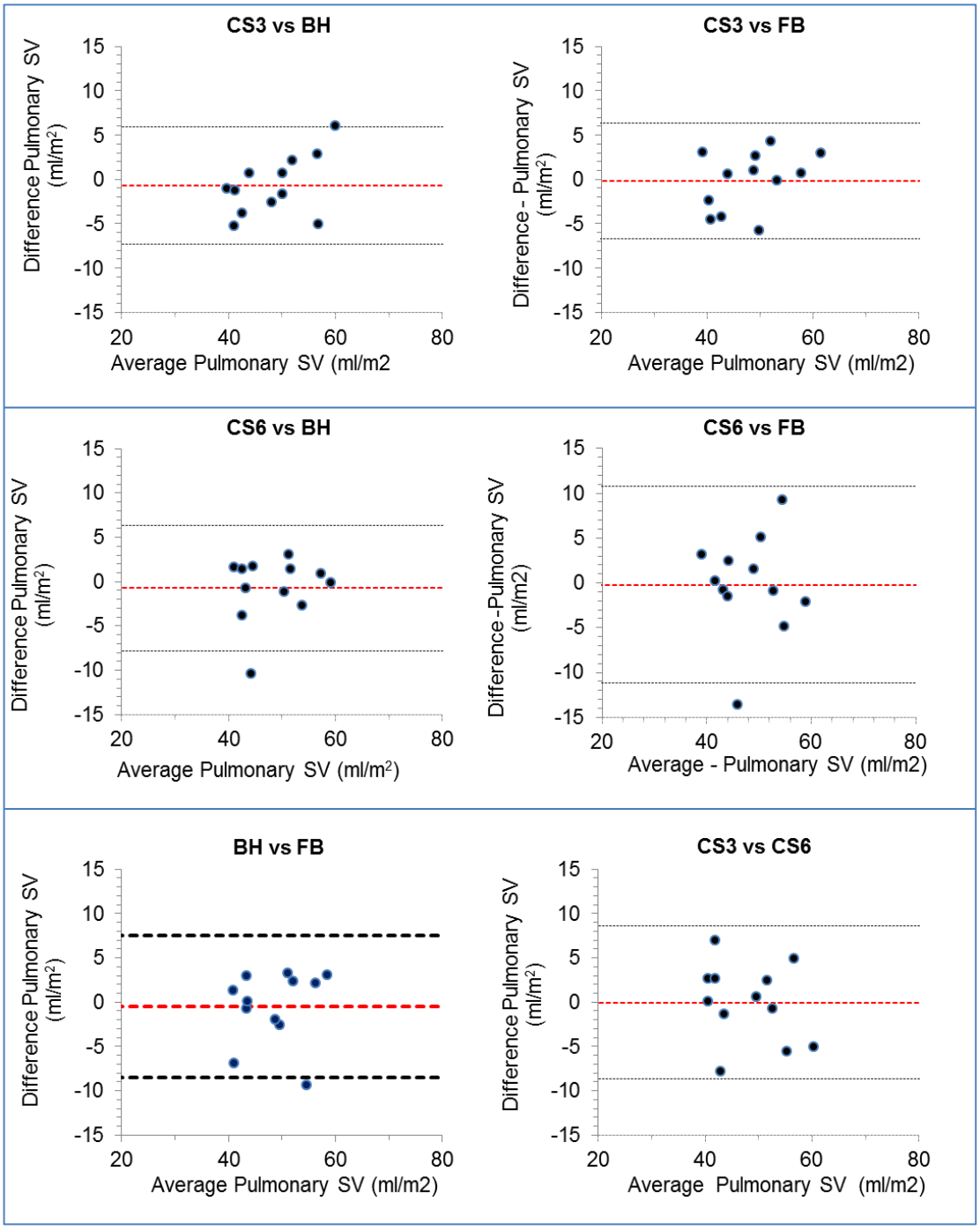


Figure 2-7 Bland Altman plots comparing resting indexed pulmonary stroke volumes Dashed red line represents mean bias (mean difference in cardiac parameter between the CS3 and clinical sequences). Dashed black lines represent the 95% limits of agreement. Pulmonary stroke volumes (SV) (ml/m^2/cardiac cycle) derived from breath held (BH), free breathing (FB), Compressed SENSE 3 (CS3) and Compressed SENSE 6 (CS6) pulmonary phase contrast magnetic resonance sequences.

2.4.2 Image quality scoring

Examples of images defined into excellent (3), good (2), adequate (1) and non-diagnostic (0) image quality categories are presented in Figure 2-8 and the different image quality scores between sequences at rest and during Ex-CMR presented in Table 2-3. As expected, resting clinical breath-hold image quality scores for aortic and pulmonary flows were significantly higher compared to free-breathing sequences ($p<0.01$), except when compared with CS3 pulmonary flow ($p=0.06$). At rest, CS3 flow sequences had the highest image quality scores of all free-breathing sequences, including the free-breathing clinical sequence, and scores were significantly greater than CS6 sequences for aortic ($p=0.02$) and pulmonary ($p<0.01$) flow. Figure 2-9 demonstrates the image quality of the different resting flow images acquired in the same patient. During exercise the image quality scores of CS3 aortic and pulmonary flow sequences were consistently higher than CS6 flow sequences. Indeed at moderate exercise intensity, five aortic and two pulmonary flow CS6 sequences were considered non-diagnostic, whereas all CS3 flow sequences were of adequate diagnostic quality. Due to the non-diagnostic image quality described in numerous CS6 flow acquisitions at moderate exercise intensity, the CS6 flow sequences were deemed unsuitable for Ex-CMR flow assessment and future studies.

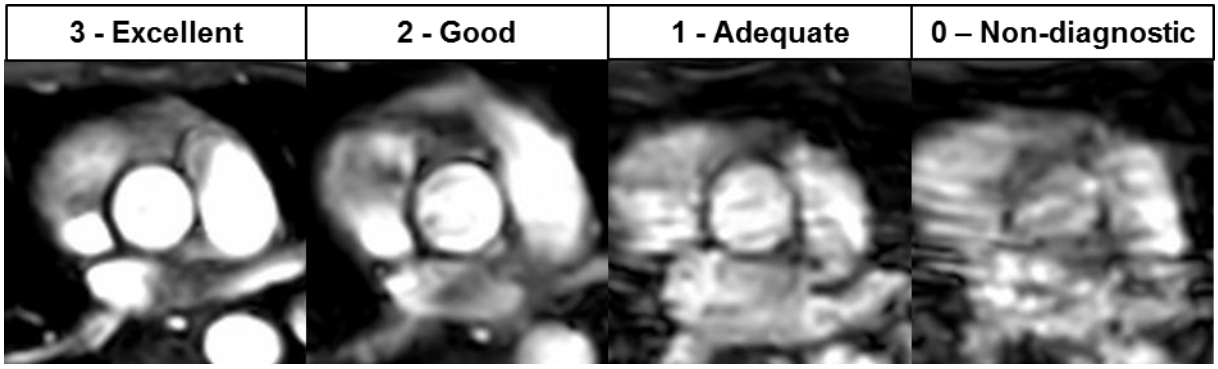


Figure 2-8 Example of image quality scoring of excellent, good, adequate and non-diagnostic aortic phase contrast magnetic resonance imag

Table 2-3 Image quality score comparison between flow sequences at rest and exercise

Flow sequence	Resting		Low exercise		Moderate exercise	
	Aortic	Pulmonary	Aortic	Pulmonary	Aortic	Pulmonary
Clinical BH	2.83±0.24*+#	2.88±0.30*#				
Clinical FB	2.21±0.38	2.08±0.45#				
CS3 FB	2.33±0.3#	2.38±0.58#	1.5±0.41#	1.46±0.62#	1.21±0.25#	1.08±0.19
CS6 FB	1.75±0.32	1.63±0.30	1.33±0.37	1.13±0.22	0.88±0.46	0.88±0.41

Image quality score: 3- excellent, 2- good, 1- adequate & 0- non diagnostic. * $p<0.05$ superior to clinical free-breathing sequence at same exercise stage, $^{+}$ $p<0.05$ superior to CS3 sequence at same exercise stage, $^{\#}$ $p<0.05$ superior to CS6 sequence at same exercise stage. BH, breath held; CS, Compressed SENSE; FB, free-breathing.

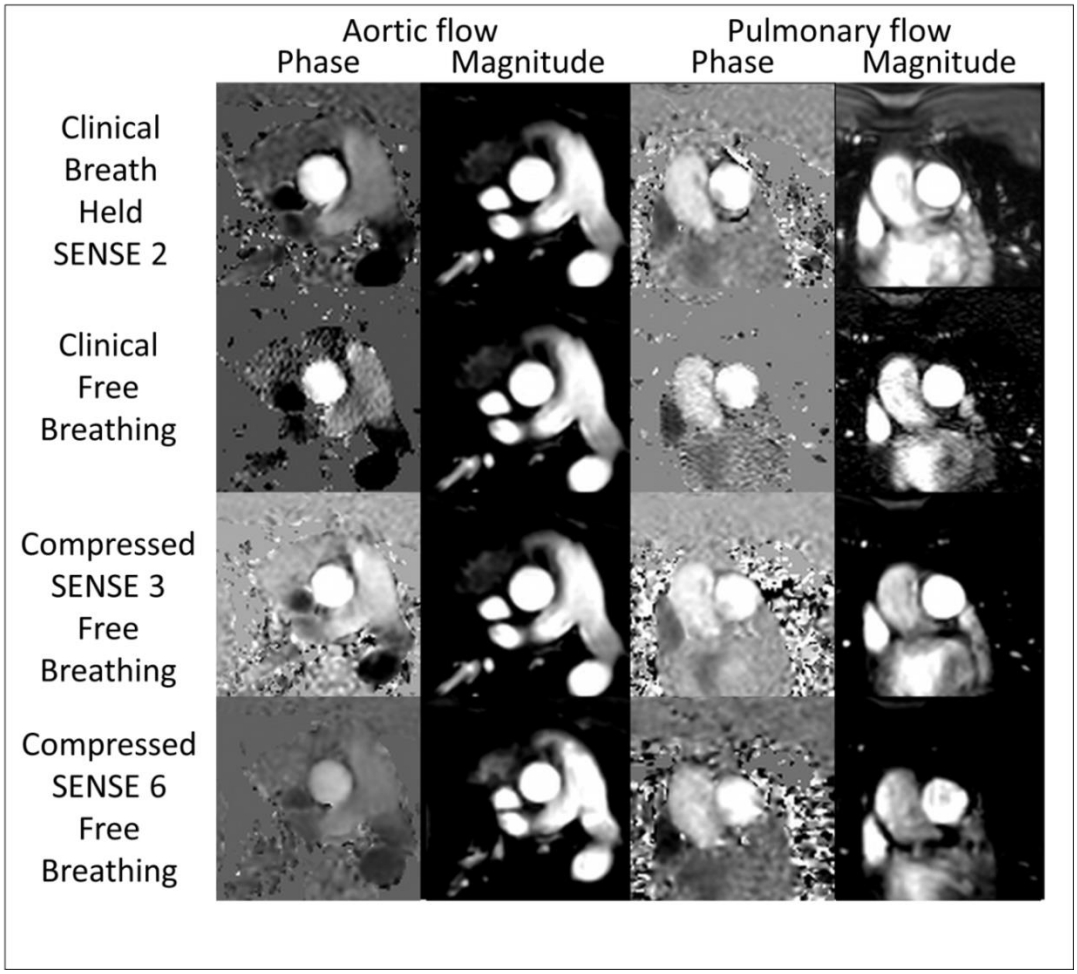


Figure 2-9 Comparison of image quality of resting phase contrast image sequences

Figure comparing both clinical standard sequences (Clinical breath held SENSE 2 & clinical free-breathing no parallel imaging) with Compressed SENSE 3 and Compressed SENSE 6 sequences.

2.4.3 Supine bicycle exercise

The participants' haemodynamic responses to supine bicycle exercise are displayed in Table 2-4. Participants' exercised for a total duration of 1947±542s (32 minutes 27 seconds ± 9 minutes 2 seconds) and maintained within the target HR during each exercise stage increasing from 58±6bpm at rest, to 102±5bpm and 119±5bpm at low and moderate exercise respectively. Systolic BP rose with increasing exercise intensity (119±10mmHg at rest to 143±15mmHg at low and

160±24mmHg at moderate exercise), whilst diastolic BP remained unchanged (71±8 mmHg at rest to 76±13mmHg at low and 75±13 mmHg at moderate exercise). BP was un-recordable at moderate exercise intensity in two subjects. Participants subjective RPE on the Borg scale (320) were 9.6±1.8 for low and 13.7±2.4 for moderate exercise intensities, falling into the target ranges, as per American College of Sports Medicine guidelines (201), for the prescribed exercise intensities. Therefore, both the objective haemodynamic and the subjective Borg RPE scores were within the advised ranges for the prescribed exercise intensities.

2.4.4 Cardiac indices response to exercise

2.4.4.1 Biventricular volumes

Table 2-4 demonstrates the cardiac volumetric and flow changes during exercise and Figure 2-10 shows the typical image quality obtained during exercise for both cine and aortic and pulmonary PCMR images.

During Ex-CMR, LVEDVi did not significantly alter (88.5±16ml/m^2 at rest, 88.2±15ml/m^2 at low an 85.9±14ml/m^2 at moderate exercise, p=0.256 for rest to moderate exercise), indexed LV stroke volume (LVSVi) increased significantly (50±7ml/m^2 at rest, 57.2±8ml/m^2 at low and 59.5±7ml/m^2 at moderate exercise; p<0.001 for rest to moderate exercise) driven by a significant fall in indexed LV end-systolic volume (LVESVi) (38.4±11ml/m^2 at rest vs 31±10ml/m^2 at low and 26.4±10ml/m^2 at moderate; p<0.001 for rest to moderate exercise) thus causing a rise in LVEF with exercise (57±6% at rest, 66±7% at low and 70±8% at moderate exercise; p<0.001 for rest to moderate exercise). Therefore, similar to a recent meta-analysis (251), results demonstrate no significant change in LVEDVi, but that LVEF is increased during Ex-CMR due to significant decreases in LVESVi.

During Ex-CMR, indexed right ventricular end-diastolic volume (RVEDVi) decreased significantly (89.8±15ml/m^2 at rest, 87.2±15ml/m^2 at low and 85.2±14ml/m^2 at moderate exercise, p=0.023 rest to moderate exercise), indexed right ventricular end-systolic volume (RVESVi) decreased (40.4±10ml/m^2 at rest vs 31.1±10ml/m^2 at low and 25.8±8ml/m^2 at moderate exercise; p<0.001 for rest to

moderate exercise) driving a rise in indexed right ventricular stroke volume (RVSVi) (49.4±7ml/m^2 at rest, 56.1±7ml/m^2 at low and 59.4±7ml/m^2 at moderate exercise; $p<0.001$ for rest to moderate exercise) and RVEF (56±6% vs 65±7% at low and 70±6% at moderate exercise; $p<0.001$ for rest to moderate exercise) with increasing exercise. Therefore during Ex-CMR, RVEF increased due to a more exaggerated decrease in RVESVi than occurred in RVEDVi.

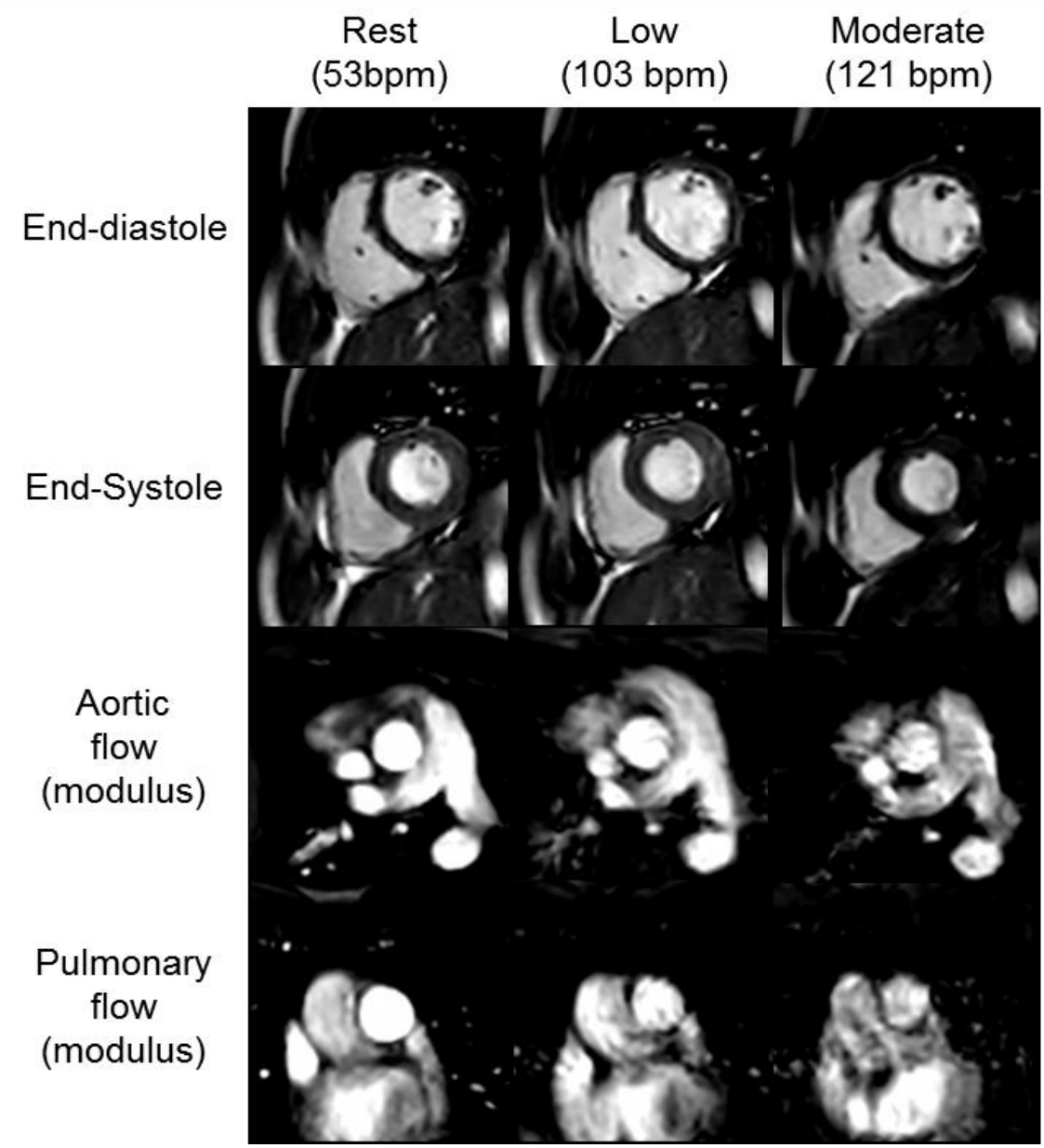


Figure 2-10 Typical image quality of cine and phase contrast imaging at rest and during Ex-CMR at low and moderate exercise using Compressed SENSE-3 sequences.

Table 2-4 Haemodynamic response to supine bicycle exercise using the C-SENSE 3 protocol

	Rest	Low intensity	Moderate intensity	ANOVA P-value	Rest vs Low	Low vs Mod	Rest vs Mod
HRR% of HR_{max}	N/A	30-39%	40-59%				
HR (bpm)	58±6	102±5	119±5	<0.001	<0.001	<0.001	<0.001
Systolic BP(mm/Hg)*	119±10	143±15	160±24	<0.001	0.001	0.038	<0.001
Diastolic BP(mm/Hg)*	71±8	76±13	75±13	0.605	1	1	1
Borg RPE	6±0	9.6±1.8	13.7±2.4	<0.001	<0.001	<0.001	<0.001
Cycle workload (W)	0	52±26	84±24	<0.001	<0.001	<0.001	<0.001
LVEDV (ml)	164±39	163±36	159±34	0.052	1	0.187	0.192
LVEDVi (ml/m^2)	88.5±16	88.2±15	85.9±14	0.066	1	0.173	0.256
LVESV (ml)	71±23	58±21	49±20	<0.001	0.001	0.001	<0.001
LVESVi (ml/m^2)	38.4±11	31±10	26.4±10	<0.001	0.001	0.001	<0.001
LVSV (ml)	93±19	106±19	110±19	<0.001	0.002	0.193	<0.001
LVSVi (ml/m^2)	50±7	57.2±8	59.5±7	< 0.001	0.002	0.177	<0.001
LVEF (%)	57±6	66±7	70±8	<0.001	<0.001	0.002	<0.001
Aortic SV (ml)	89±17	102±18	105±18	<0.001	0.001	0.708	<0.001
Aortic SVi (ml/m^2)	48.2±7	55.1±8	56.6±8	<0.002	0.001	0.682	<0.001
RVEDV (ml)	166±34	161±33	158±31	0.003	0.104	0.18	0.025
RVEDVi (ml/m^2)	89.8±15	87.2±15	85.2±14	0.002	0.096	0.16	0.023
RVESV (ml)	75±21	58±20	48±17	<0.001	<0.001	0.001	<0.001
RVESVi (ml/m^2)	40.4±10	31.1±10	25.8±8	<0.001	<0.001	0.001	<0.001
RVSV (ml)	91±17	104±18	110±17	<0.001	<0.001	0.008	<0.001
RVSVi (ml/m^2)	49.4±7	56.1±7	59.4±7	<0.001	<0.001	0.008	<0.001
RVEF (%)	56±6	65±7	70±6	<0.001	<0.001	<0.001	<0.001
Pulmonary SV (ml)	89±18	100±17	102±16	<0.001	0.007	1	0.012
Pulmonary SVi (ml/m^2)	48.2±8	54.3±7	55.2±7	<0.001	0.005	1	0.009

Abbreviations: BP, blood pressure; BPM, beats per minute; EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; HR, heart rate; HRR, heart rate reserve; i, Indexed to body surface area; LV, left ventricle; RPE, rate of perceived exertion; RV, right ventricle; SV, stroke volume; W, Wat

2.4.4.2 Flow

Aortic stroke volumes increased significantly during Ex-CMR from 48.2±7ml/m^2/cardiac cycle at rest to 55.1±8ml/m^2/cardiac cycle at low and 56.6±8ml/m^2/cardiac cycle at moderate exercise intensities ($p<0.001$, rest to moderate exercise). Indexed aortic stroke volumes showed very strong correlation with LVSVi at rest ($r= 0.93$), low ($r= 0.97$) and moderate exercise ($r= 0.98$). During Ex-CMR pulmonary stroke volumes increased significantly from 48.2±8ml/m^2/cardiac cycle at rest to 54.3±7ml/m^2/cardiac cycle at low and 55.2±7ml/m^2/cardiac cycle at moderate exercise intensities ($p=0.009$, rest to moderate exercise) and correlated strongly with RVSVi at rest ($r= 0.88$) and very strongly during low ($r= 0.90$) and moderate exercise ($r= 0.97$). However, close correlation of stroke volumes acquired from PCMR and cine sequences is not unexpected given both are assessing similar indices.

2.4.5 Intra/Inter-observer reproducibility

Intra- and inter-observer reproducibility is shown in Table 2-5. Intra-observer reproducibility of all cardiac sequences assessed at rest and during exercise by CV were excellent (CV<10%) and all sequences assessed by ICC were excellent (ICC>0.9) with exception of pulmonary flow at low (ICC = 0.892) and moderate exercise (ICC= 0.847) and LVSV at moderate exercise (ICC = 0.897).

Inter-observer reproducibility assessed by CV of cardiac parameters were similarly excellent (CV<10%), with the exception of RVESV by CS3 cine imaging at rest (CV 12.96%) and LVESV and RVESV during exercise, with a CV of 11.38% and 11.39% at low and 16.61% and 17.93% at moderate exercise intensities respectively. Cardiac parameters demonstrated excellent ICC (>0.9) at rest with the exception of RVSV & RVEF on clinical sequences and RVESV, RVSV & RVEF on CS3 sequences demonstrating good ICC (>0.8). During low intensity exercise all cardiac parameters demonstrated excellent ICC (>0.9), which decreased to good ICC at moderate exercise (ICC>0.75) with the exception of LVEDV and aortic flow which maintained excellent ICC (>0.9). The increase in variability of end-systolic volumes with increased exercise intensity is unsurprising given the significant fall in ESV with exercise which allows for a smaller margin of error.

Table 2-5 Reproducibility of biventricular volumetric and flow indices

Exercise level and sequence	Cardiac Parameter	Intra-observer		Inter-observer	
		CV	ICC	CV	ICC
Resting Clinical	LVEDV	1.32	0.996	2.12	0.988
	LVESV	2.69	0.989	6.58	0.968
	LVSV	2.47	0.967	4.24	0.920
	LVEF	2.06	0.987	3.75	0.931
	RVEDV	2.29	0.985	2.65	0.979
	RVESV	5.34	0.968	8.60	0.918
	RVSV	3.94	0.953	6.89	0.808
	RVEF	3.55	0.957	6.35	0.877
	Aortic flow FB	1.14	0.990	3.07	0.930
	Aortic flow BH	0.83	0.997	2.05	0.980
	Pulmonary flow FB	1.18	0.993	2.15	0.973
	Pulmonary flow BH	1.40	0.988	1.78	0.981
Resting Compressed SENSE 3 Free-breathing	LVEDV	1.29	0.995	2.50	0.985
	LVESV	3.89	0.976	6.66	0.965
	LVSV	2.89	0.958	3.44	0.942
	LVEF	2.98	0.974	3.41	0.953
	RVEDV	1.92	0.986	4.15	0.937
	RVESV	5.40	0.957	12.96	0.814
	RVSV	3.67	0.945	6.24	0.824
	RVEF	3.23	0.968	7.26	0.817
	Aortic flow	0.83	1.000	1.19	0.993
	Pulmonary flow	2.19	0.986	3.55	0.950
Low intensity exercise Compressed SENSE 3 free-breathing	LVEDV	0.76	0.998	3.97	0.953
	LVESV	8.77	0.915	11.38	0.911
	LVSV	4.44	0.907	3.46	0.952
	LVEF	4.72	0.923	4.08	0.916
	RVEDV	1.95	0.984	3.72	0.955
	RVESV	8.78	0.907	11.39	0.909
	RVSV	2.97	0.947	3.07	0.940
	RVEF	4.37	0.934	4.09	0.908
	Aortic flow	1.99	0.986	5.88	0.917
	Pulmonary flow	3.13	0.892	3.84	0.927
Moderate intensity exercise Compressed SENSE 3 free-breathing	LVEDV	2.09	0.986	4.27	0.940
	LVESV	9.50	0.952	16.61	0.883
	LVSV	4.17	0.897	4.37	0.849
	LVEF	3.54	0.956	4.96	0.891
	RVEDV	3.48	0.964	5.77	0.878
	RVESV	9.23	0.926	17.93	0.754
	RVSV	3.77	0.923	4.99	0.830
	RVEF	2.95	0.955	5.12	0.837
	Aortic flow	2.22	0.975	4.01	0.918
	Pulmonary flow	6.22	0.847	6.11	0.879

Abbreviations: CV, co-efficient of variance; Breath held; EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; FB, free breathing; HR, heart rate; i, Indexed to body surface area; ICC, intra-class correlation; LV, left ventricle; RV, right ventricle.

2.5 Discussion

This study has shown that 1) free breathing CS3 sequences provide acceptable image quality and comparable assessment of biventricular size/function and flow to standard clinical sequences at rest 2) it is feasible to assess biventricular volumes and flow by CMR during continuous in-scanner supine bicycle exercise using free-breathing C-SENSE, 3) Using CS3 compared to standard clinical imaging, image quality and reproducibility were good, but this was not the case with higher acceleration factors (CS6) and 4) Using CS3, we have shown superior reproducibility in comparison to the only previous study to perform biventricular volume and flow assessment during continuous Ex-CMR (which used un-gated real-time sequences) (268).

To our knowledge, only one prior study, by Jaijee *et al*, has assessed biventricular volume and flow assessment with free-breathing during continuous exercise, and did so by utilising an un-gated real-time technique (268). The study was insightful, investigating right ventricular dysfunction in acute hypoxia and chronic pulmonary arterial hypertension. However the authors didn't perform image quality assessment and demonstrated suboptimal reproducibility, on the basis of ICC for intra- and inter-observer variability for RVEF. Our RVEF ICC for intra- and inter-observer analysis respectively was 0.968 and 0.817 at rest, and 0.955 and 0.837 at moderate exercise (vs 0.71 and 0.85 at rest and 0.625 and 0.744 at moderate exercise in the un-gated real-time study). One caveat with this direct comparison is we only studied healthy volunteers in this study, whereas Jaijee *et al* studied healthy volunteers and patients with pulmonary hypertension (268); patients may demonstrate increased respiratory motion, worse image quality and so a resultant decrease in reproducibility. Therefore our technique needs testing in patients with cardiac disease before direct comparisons can be confidently made. Both studies represent a significant progression in the potential clinical utility of Ex-CMR, however our study is the first study to demonstrate such feasibility using vendor provided sequences with analysis performed on standard commercially available software.

Comparatively lower heart rates are observed during supine exercise compared with upright exercise at the same intensity. Exercise in the supine position results in higher blood pressure than upright exercise (227), therefore a similar double product (systolic blood pressure x heart rate), which is an index of myocardial oxygen consumption (321), is achieved at lower heart rates than upright exercise (210, 217, 226). Therefore, we used HRR to determine subject specific THR, with the resting heart rate assessed when supine. Importantly, our study aimed only to assess subjects to moderate exercise intensity, and not to submaximal or maximal intensity. Maximal in-scanner continuous exercise can create significant motion artefacts, rendering images non-diagnostic, but more importantly may be unsafe in a patient population, given the inability to accurately assess ST segment changes which could prompt test termination. However, even at moderate intensity exercise, an Ex-CMR protocol assessing biventricular function and flow, may theoretically provide additional diagnostic and prognostic information in valvular and congenital heart disease, especially for valvular regurgitation assessment.

2.5.1 Biventricular response to exercise

The haemodynamic response to exercise demonstrated a minimal change in LVEDV and a rise in LVSV driven by a fall in LVESV during exercise, which is in keeping with a recent Ex-CMR meta-analysis of 16 Ex-CMR studies (251). Indeed, our study demonstrated a non-significant decrease in LVEDV with exercise as was demonstrated by the majority of Ex-CMR studies in the Ex-CMR meta-analysis. These findings replicate the theory that being truly supine (rather than recumbent in stress echocardiography) results in near maximal LVEDV at rest and thus no significant increase is seen with exercise. Additionally, in keeping with prior supine Ex-CMR studies (93, 250, 268, 322), the right ventricular response to supine Ex-CMR in healthy volunteers in our study demonstrated decreases in RVEDVi, with a more significant decrease in RVESVi resulting in rises in RVSVi and RVEF.

2.6 Clinical Implications

The clinical utility of Ex-CMR requires rapid image acquisition using accessible free-breathing sequences and analysis software. We demonstrated this is feasible using C-SENSE. C-SENSE is a vendor provided, CE-MARK'ed pulse sequence, permitting faster image acquisition (295, 296) and greater robustness to respiratory motion (297) than standard parallel imaging techniques. Our C-SENSE protocol's ability to assess biventricular haemodynamics and great vessel flow, which could be used to quantify valvular forward flow/regurgitant flow, in response to incremental exercise could theoretically allow a comprehensive assessment in valvular and congenital heart disease. Further research in these patient cohorts is required. In asymptomatic significant valve disease, ventricular dilatation/dysfunction or an abnormal exercise response can guide the decision to advise intervention (1, 37). Given CMR is the reference standard for biventricular assessment and CMR derived aortic and mitral regurgitation quantification displays superior prognostic value to transthoracic echocardiography (63, 64, 292), the additional assessment during exercise may theoretically provide further prognostic information. Additionally, in-scanner MR-CPET is feasible (253) and our protocol could be performed in combination, theoretically creating a single comprehensive investigation. C-SENSE acceleration may benefit other Ex-CMR applications. For example, free breathing first pass perfusion using compressed sensing at rest (323) and supine exercise stress perfusion CMR are both feasible (223), therefore C-SENSE accelerated Ex-CMR stress perfusion may also be feasible. Our technique requires further research to demonstrate feasibility in patient populations, assess if additional prognostic information is provided above a resting CMR scan and whether C-SENSE can be used for other Ex-CMR applications.

2.6.1 Relevance of study findings in field of Ex-CMR

Ex-CMR, although niche, is a larger field of imaging and research than is appreciated with over 70 publications in the field. As discussed in Chapter 1.2, numerous exercise modalities exist and numerous diseases have been investigated from coronary artery disease and congenital heart disease to diabetic

heart disease. The majority of Ex-CMR studies assessing non-ischaemic heart disease have done so using cine imaging or PCMR. Despite this and the significant developments in Ex-CMR over the past 3 decades only one prior study (268), discussed above, has successfully performed combined biventricular cine imaging and PCMR flow assessment of the aortic/pulmonary valves/vessels. This is largely in part due to the difficulty of performing imaging of sufficient quality and fast enough to acquire the data in the limited time available prior to the onset of leg fatigue in the exercising patient. This was feasible in our study due to faster image acquisition afforded by the use of C-SENSE sequences. Our developed protocol is a significant step forward in the field, as it allows assessment of biventricular function and great vessel flow, whilst using widely attainable sequences and without the need for specialist software. The protocol could now be used to assess a wide range of structural heart disease. Most importantly, the ability to quantify aortic, mitral, pulmonary and tricuspid regurgitation, in the same protocol, during exercise significantly opens the door for valvular assessment by Ex-CMR. Hopefully the developed protocol will facilitate multiple future Ex-CMR studies in a broad range of structural and valvular diseases, with the eventual aim that Ex-CMR form part of routine clinical assessment in valve disease patients with borderline severe disease where accurate exercise imaging can assist decision making.

2.6.2 Novelty of study findings

This study has multiple novel aspects and findings, specifically being the first study to: use C-SENSE with Ex-CMR, assess the optimal C-SENSE acceleration factor for PCMR sequences for use in CMR/Ex-CMR and to validate an Ex-CMR protocol assessing biventricular volumes and flow using commercially available equipment, software and retrospective gating techniques.

This is the first study to use C-SENSE with Ex-CMR and demonstrate its feasibility in the field. Although Jaijee et al previously demonstrated feasibility of performing free breathing acquisition of biventricular volumes/function and great vessel flow during continuous exercise (268), ours is the first to do so using retrospective cardiac gating techniques, with the benefits of increased widespread attainability

already discussed. Therefore ours is the first study to validate an Ex-CMR protocol assessing biventricular volumes and flow using easily acquirable commercially available software and equipment that can assess a broad range of structural cardiac disease. To the best of knowledge, this is the first study to investigate the optimal C-SENSE acceleration factor for PCMR sequences, in terms of image quality and flow correlation with reference standard, for use in CMR/Ex-CMR. Our findings have implications for future Ex-CMR studies but also provide novel insight for resting imaging. Indeed, the finding that CS6 free breathing aortic sequences underestimate aortic flow may be of importance to those using higher acceleration factors in resting clinical imaging.

2.7 Study limitations

The study sample size is small and in healthy volunteers with a healthy mean BMI (23.9±2.3 kg/m^2) and a mean age (35±9 years) younger than patients typically referred for exercise cardiac imaging. Supine Ex-CMR is feasible in older patients (93, 241, 290, 324) and obese patients (249) but may be tolerated less well than by our study population, potentially resulting in more respiratory and motion artefacts. Thus our technique requires further evaluation in patients with cardiovascular disease. As with prior supine Ex-CMR studies using a cycle ergometer (93), knee-to-bore clearance can restrict use in very tall patients. However, height was not an exclusion criteria in this study, with the tallest patient at 182cm. Additionally, all patients tolerated the Ex-CMR protocol well, completing the imaging without any significant restrictions to performing exercise in the scanner bore. Exercise duration in the study was longer than ideal for clinical use, but this was a feasibility and validation study, testing numerous sequences therefore prolonging exercise duration. Further adaption would be required to reduce exercise times for clinical use. This could be achieved by removing sequences depending on the aims and/or by removing the low intensity exercise stage and just imaging at rest and moderate exercise. Derived volumes and flow from biventricular cine images and phase contrast images respectively were not compared directly with the reference standard of the direct Fick method, however as we have demonstrated, the

biventricular cine and corresponding phase contrast flow stroke volumes correlated very strongly, demonstrating the internal validity of our technique. Additionally, our results follow prior supine Ex-CMR studies, as demonstrated in a recent meta-analysis (251), demonstrating rising stroke volumes with increasing exercise driven by a fall in LVESV but minimal change in LVEDV. Inter-scan reproducibility was not assessed with this study, but has been demonstrated in our institution previously in an Ex-CMR study assessing biventricular volumes using a similar retrospectively gated, respiratory navigated short axis cine sequence (93). As expected, and demonstrated in prior Ex-CMR studies (230, 250-252), image quality decreases with increasing exercise intensity, however our study still demonstrated good intra- and inter-observer reproducibility during moderate intensity exercise. ECG interference was encountered in one patient, early in the study, such that miss-triggering occurred at moderate exercise intensity. This made analysis technically unfeasible and so the subject was excluded from the study. Subsequent subjects had pulse oximetry attached as a backup cardiac gating technique should ECG interference occur, however this was not required.

2.8 Conclusion

Assessment of biventricular function, aortic and pulmonary flows during continuous exercise is feasible during exercise to moderate intensity using a free-breathing C-SENSE accelerated protocol. The ability to use commercially available analysis software with this vendor provided technique increases the potential clinical utility of Ex-CMR. The developed protocol allows the direct quantification of flow across the aortic and pulmonary valves and indirect quantification of mitral and tricuspid regurgitation during exercise. Further evaluation is needed in patients with cardiovascular disease to assess the value and reproducibility in a clinical setting.

Chapter 3

Feasibility of biventricular volume assessment and MR quantification in primary MR patients during supine exercise cardiovascular magnetic resonance

3.1 Abstract

Background

Biventricular volume and great vessel flow assessment during continuous supine free-breathing supine Ex-CMR has recently been demonstrated feasible using Compressed SENSE-3 (CS3) sequences. Exercise transthoracic echocardiography (TTE) provides additional prognostic information in primary mitral regurgitation (MR). Resting CMR offers reference standard biventricular assessment and MR quantification with superior reproducibility to TTE. Therefore, we aimed to determine the feasibility of biventricular assessment and MR quantification in primary MR patients using the recently validated Ex-CMR protocol.

Methods

10 patients with at least moderate primary MR on TTE (8 male, age 62, 55-67years IQR) underwent an Ex-CMR protocol involving free-breathing CS3 respiratory navigated short axis cine imaging and free-breathing CS3 aortic phase-contrast magnetic-resonance at rest and during individually prescribed low and moderate intensity in-scanner (1.5T Philips Ingenia) supine cycle ergometer exercise (Lode BV). Intra/inter-observer reproducibility of cardiac indices was assessed by coefficient of variance (CV). Images were analysed on commercially available software (Circle, CVi)

Results

All patients completed the Ex-CMR protocol with no complications. During exercise, there were no statistically significant changes in biventricular volumes or global left ventricular ejection fraction (LVEF). From rest to low and moderate

exercise: right ventricular ejection fraction increased (55±5.4% to 60±6.0% and 63±6.6% respectively, p=0.001), mitral regurgitant fraction (MR-RF) decreased (40±14% to 36±11% and 30±15% respectively, p=0.006) and effective forward LVEF increased (38±9.3% to 43±9.3% and 46±11% respectively, p=0.004), which is a composite of aortic stroke volume and left ventricular end-diastolic volume. Intra-observer reproducibility was excellent (CV <10%), except right ventricular stroke volumes (RVSV) during low and right ventricular end-systolic volumes (RVESV) during both exercise stages, which were good (CV10-20%). Inter-observer reproducibility was excellent (CV<10%), except RVESV and mitral regurgitant volumes at all stages, left ventricular end-systolic volumes during low and MR-RF during moderate exercise, which were good (CV 10-20%).

Conclusion

Biventricular assessment and MR quantification during continuous supine Ex-CMR is feasible and reproducible in asymptomatic primary MR patients. The use of vendor provided sequences and commercially available software increases the widespread attainability and potential clinical utility of the technique. Further research assessing the techniques prognostic ability in primary MR patients is now warranted.

3.2 Introduction

The appropriate timing of surgical intervention in patients with significant primary mitral regurgitation is difficult and currently guided by symptom development and/or risk stratification by cardiac imaging (1, 39). However, onset of symptoms in chronic valve disease can be slow/indolent and patients may be unaware of subtle changes in exercise tolerance, even on direct questioning (78). Exercise imaging is therefore beneficial to accurately identify patients with a symptomatic response or imaging biomarkers that may benefit from early surgical intervention (1, 39, 78). Exercise-TTE is useful to risk stratify patients (1, 37), during which, the absence of LV contractile reserve (LVCR) (85, 86), limited RV contractile recruitment (87), an increase in MR severity (88) or exercise induced pulmonary hypertension (89, 90) are predictive of a poorer prognosis. Unfortunately, even in the research setting, suboptimal acoustic windows can prevent stress echocardiography use in ~10% of patients (88). This deteriorates further in the 'real world' setting, where the feasibility of MR quantification (PISA method) during exercise-TTE was only feasible in 55% of patients, decreasing further to 43% in patients with mitral valve prolapse in a study by Coisne *et al* (92). The use of Ex-CMR could potentially overcome these issues as it is not limited by acoustic windows. Resting CMR provides reference standard biventricular assessment (51, 52) with MR quantification with superior reproducibility (59, 60, 62, 63) and prognostic ability compared to TTE (63, 64). In Chapter 2 the ability to perform biventricular volume and great vessel flow assessment during continuous supine Ex-CMR was demonstrated as feasible in healthy volunteers. This technique could provide the ability to assess biventricular response and changes in quantified MR during exercise in MR patients. Additionally the technique should allow calculation of effective forward LVEF which has never been previously assessed in MR patients during exercise before. Effective forward LVEF is a composite of LVEDV and aortic stroke volumes, which allows accurate determination of forward LV pump efficiency even in the presence of severe MR and has demonstrated accurate predictive value of determining post-operative LVEF in primary MR patients during a prior resting CMR study (325). Supine Ex-CMR in primary MR patients is feasible. Previous work by Chew *et al*, demonstrated feasibility of biventricular volume

assessment during supine Ex-CMR in 5 degenerative MR patients, however simultaneous exercise PCMR aortic flow assessment was not performed, preventing quantification of MR during exercise (93). Given that a dynamic increase in MR during exercise is associated with poorer outcomes (88), the ability to simultaneously accurately assess cardiac reserve and quantitate MR changes during Ex-CMR is appealing and could potentially overcome limitations described in exercise-TTE.

3.3 Aims

This study aimed to 1) demonstrate the feasibility of assessing biventricular volumes and MR quantification in asymptomatic primary MR patients during continuous supine Ex-CMR, using vendor provided image sequences and commercially available analysis software (Circle CVi) (as developed in chapter 2), 2) assess the reproducibility of the acquired biventricular volumes and quantitated MR-Rvol and MR-RF by performing intra/inter-observer analysis and 3) describe the biventricular and quantitated MR changes during supine Ex-CMR in asymptomatic primary MR patients.

3.4 Methods

3.4.1 Study design and population

Patients were prospectively recruited from the specialist valve clinic at the Leeds Teaching Hospitals NHS Trust. Inclusion criteria: At least moderate primary MR with LVEF>55% on TTE and asymptomatic (NYHA functional class I). Exclusion criteria: Secondary MR (atrial, ischaemic, functional), significant aortic valve disease on TTE (≥moderate severity), presence of AF, prior myocardial infarction, significant respiratory disease and any contraindications to exercise stress testing according to AHA guidelines (222). At least moderate MR severity on baseline TTE was defined by integrative approach using ASE guidelines (40), with severity parameters as described in Table 1-2.

This study was approved by a local ethics committee in England (Yorkshire and the Humber – Leeds East **18/YH/0168)**. All participants provided written informed consent. All Ex-CMR studies were performed at the Leeds General Infirmary, UK (See appendix).

3.4.2 Exercise protocol

The exercise protocol used is identical to that utilised in healthy volunteers in Chapter 2 and is described in depth in Chapter 2.3.4. In brief summary: patients underwent unloaded (0W) cycling for 1-minute on the Lode BV supine ergometer with subsequent increases of 25W every 2-minutes until low intensity THR achieved (30-39% HRR). Maintenance of THR for exercise stage was made by small alterations in resistance if required and THR stabilised for 30 seconds prior to CMR imaging. After completion of resting imaging, the 'ramping' process was repeated increasing resistance by 25W every 2-minutes until moderate intensity THR achieved (40-59% HRR) and heart rate stable for 30 seconds before CMR imaging.

3.4.3 CMR imaging

The CMR imaging performed in this study utilised the CS3 protocol developed and validated in healthy volunteers in Chapter 2. Pulmonary PCMR sequences validated in the healthy volunteers were omitted from this study, to reduce scan/cycle time and as they are not required to quantitate MR. CMR imaging was performed on a dedicated cardiovascular 1.5 Tesla MRI system (Philips Ingenia system, Best, Netherlands). Initial resting survey and cine imaging was performed including: vertical long axis, horizontal long axis, LVOT 1&2 views. Respiratory navigated CS3 short axis cine imaging and CS3 aortic PCMR stack, with planning centred around the sino-tubular junction (Figure 2-2), were performed at rest, low and moderate exercise intensity, during free breathing continuous exercise. Free-breathing 4-chamber and LVOT images were re-acquired at each exercise stage to allow re-planning of the CS3 SA cines and aortic PCMR stack if required. CS3

CMR sequence parameters were identical to those developed in Chapter 2 and are described in-depth in Chapter 2.3.4.2.

3.4.4 CMR analysis

Images were analysed using commercially available software (cvi42, Circle Cardiovascular Imaging, Calgary, AB, Canada). LV and RV endocardial contours were manually traced with the papillary muscles and trabeculations considered part of the ventricular blood pool and volumes calculated by summation of disks (319). Aortic flows were assessed by manually contouring the vessel endovascular wall in every phase. The CS3 aortic PCMR stack was assessed for the slice closest resembling the resting acquisition to ensure all PCMR images had flow assessed at the same anatomical level. MR was quantitated by the indirect LVSV-AoSV method as described in Chapter 1.1.3.3.2. Effective forward LVEF was calculated by a ratio of forward aortic stroke volume and LVEDV (AoSV/LVEDV) as previously described by Gelfand *et al* (325).

3.4.5 Statistical analysis

Data were analysed using SPSS version 26 (IBM Corp.) and Microsoft Excel 2010. All continuous data were assessed for normality using Shapiro-Wilk test. The differences in continuous variables between rest, low and moderate exercise were compared by repeated measures ANOVA with Bonferroni correction for normally distributed variables and Friedman's test with Bonferroni correction (if significant) for non-normally distributed variables (326). Intra-observer analysis was performed by TC and inter-observer analysis by NJ; the reproducibility was assessed by the Coefficient of Variation test, the standard deviation of differences between observations divided by the mean. Intra and inter-observer analysis was performed in a blinded method. $p<0.05$ was considered statistically significant.

3.5 Results

3.5.1 Patient demographics

Ten patients with at least moderate MR on TTE were recruited (8 male, 2 female), with a median age of 62 years (55-67years IQR) and underwent CMR at rest and during continuous exercise using the Lode BV supine bicycle ergometer. Patient demographics are displayed in Table 3-1. Participants were of a healthy weight (BMI 24.8±3.3) and varying levels of physical fitness, with 50% performing no regular exercise and group median of 1hour/week (0-2.2hrs/week IQR). All patients had no contraindications to exercise testing as per AHA guidelines (222). The underlying aetiology of MR was PMVL prolapse in 7 patients, bileaflet prolapse in 2 patients and a congenital cleft in the anterior mitral valve leaflet in 1 patient. The majority of patients (n=8) had severe MR on baseline TTE with 1 patient with moderate-severe MR and 1 with moderate MR. In terms of prior cardio-respiratory medical history: 2 patients were hypertensive, 1 had intermittent supraventricular tachycardia and 1 suffered multiple previous pulmonary emboli. Two patients were on regular angiotensin converting enzyme inhibitors and 2 on regular beta-blockers.

Table 3-1 Baseline characteristics of patients in the CYCLE-MITRAL study

Baseline characteristics	
Age (years)	62 (55-67)
Male	8
Height (cm)	173±6.7
BMI (kg/m^2)	24.8±3.3
BSA (m^2)	1.9±0.2
Weekly exercise (hours)	1 (0-2.2)
Cardiac medications:	
Beta-blockers	2
ACE inhibitors	2
MR aetiology:	
PMVL prolapse	7
AMVL prolapse	0
Bileaflet prolapse	2
Congenital	1
TTE defined MR severity:	
Moderate	1
Mod-Severe	1
Severe	8

Abbreviations: ACE, angiotensin converting enzyme; AMVL, anterior mitral valve leaflet; BMI, body mass index; BSA, body surface area; MR, mitral regurgitation; PMVL, posterior mitral valve leaflet; TTE, transthoracic echocardiography.

3.5.2 Baseline CMR

Resting/baseline cardiac indices on CMR assessment are displayed in Table 3-2. Baseline LVEF was preserved at 64±4.9%. On CMR assessment, baseline/resting quantitated MR categorised MR severity as: 4 with severe MR, 5 with moderate-severe MR and 1 with mild MR by Gelfand *et al* criteria (70), with a mean MR-Rvol of 56±25ml and MR-RF of 40±14%.

3.5.3 Supine bicycle exercise

The patient's haemodynamic responses to supine bicycle exercise are displayed in Table 3-2. Patients exercised for a mean total duration of 1206±303s (20 minutes 6 seconds ± 5 minutes 3 seconds), with increasing resistance from 51±16W at low to 82±10W at moderate exercise. Patients described increasing subjective RPE on the Borg scale (320) from 6±0 to 9.5±1.6 and 14.8±1.2 for rest, low and moderate exercise intensities respectively ($p<0.001$). From rest to low and moderate exercise, patients HR increased (61±10bpm vs 98±6bpm and 115±6bpm respectively, $p<0.001$), systolic BP increased (128±10mmHg to 145±16mmHg and 163±27mmHg respectively, $p=0.001$), whilst diastolic BP remained unchanged (78±9 mmHg vs 81±15mmHg and 80±9 mmHg respectively, $p=0.665$).

3.5.4 Cardiac indices response to exercise

3.5.4.1 Left ventricular indices

Changes in biventricular size/function during supine Ex-CMR are displayed in Table 3-2. From rest to low and moderate exercise, LVEDVi (112±23ml/m^2, 111±21ml/m^2 and 107±22ml/m^2 respectively, $p=0.185$), LVESVi (41±12ml/m^2, 36±9.8ml/m^2 and 37±11ml/m^2 respectively, $p=0.055$), LVSVi (71±14ml/m^2, 75±15ml/m^2 and 70±15ml/m^2 respectively, $p=0.156$) and LVEF (64±4.9%, 67±5.1% and 66±6.1% respectively, $p=0.075$) remained unchanged (Figure 3-1). As demonstrated in Figure 3-2, patients demonstrated a variable left ventricular response to exercise, with 4 patients showing the presence of LVCR (≥4% rise in LVEF), 4 patients absence of LVCR and 2 patients had an initial augmentation of LVEF≥4% at low intensity exercise, which then dropped below resting LVEF at moderate intensity, which has been termed 'partial LVCR'.

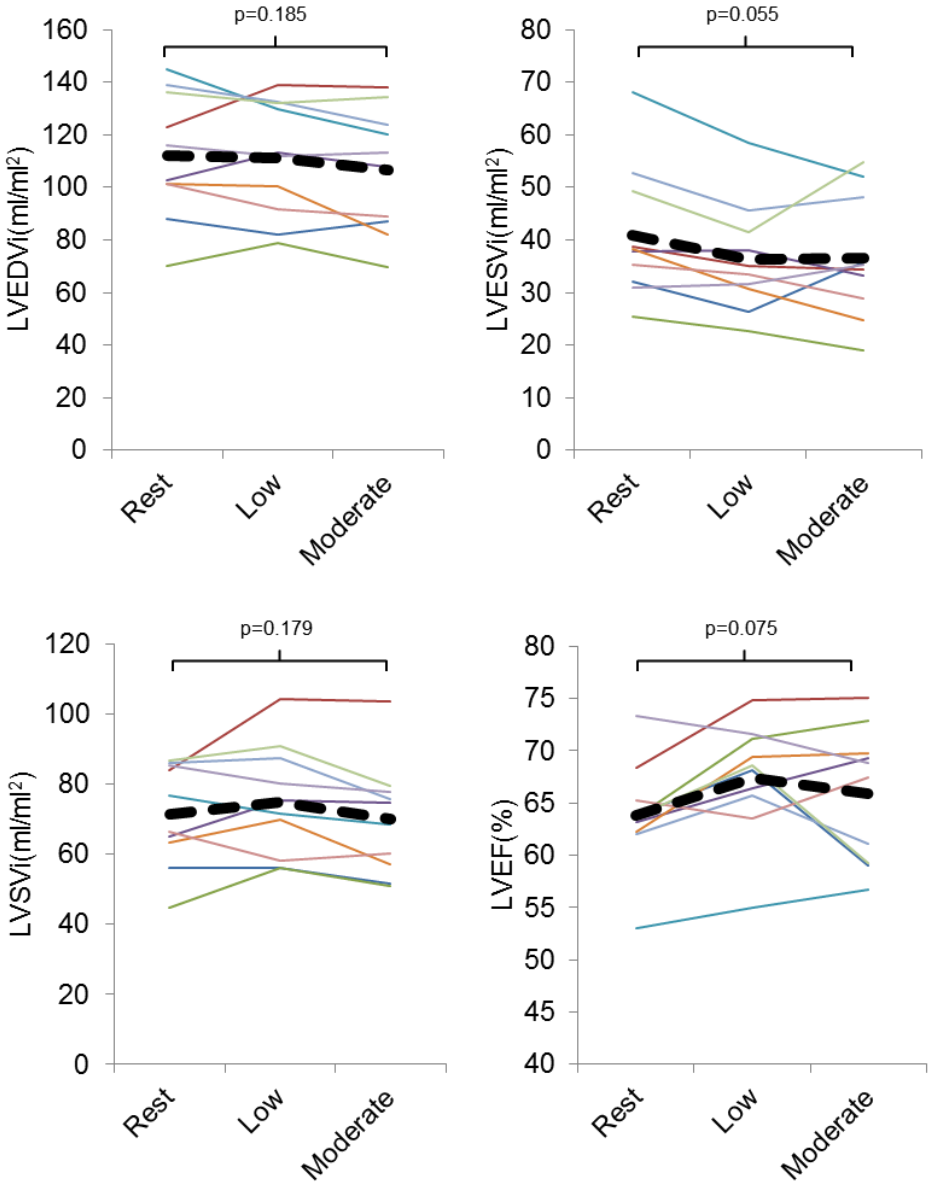


Figure 3-1 Changes in left ventricular indices during supine Ex-CMR

LVEDVi (upper-left), LVESVi (upper right), LVSVi (lower left) and LVEF (lower-right) during supine Ex-CMR. Mean group values depicted by dashed black line. Statistical comparison across all exercise stages presented (top of graph), which if significant then intergroup comparisons (rest vs low, low vs moderate and rest vs moderate exercise intensities) are presented (bottom of graph). Abbreviations: EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; Ex-CMR, Exercise Cardiovascular magnetic resonance; i, indexed to body surface area; LV, left ventricular; SV, stroke volume.

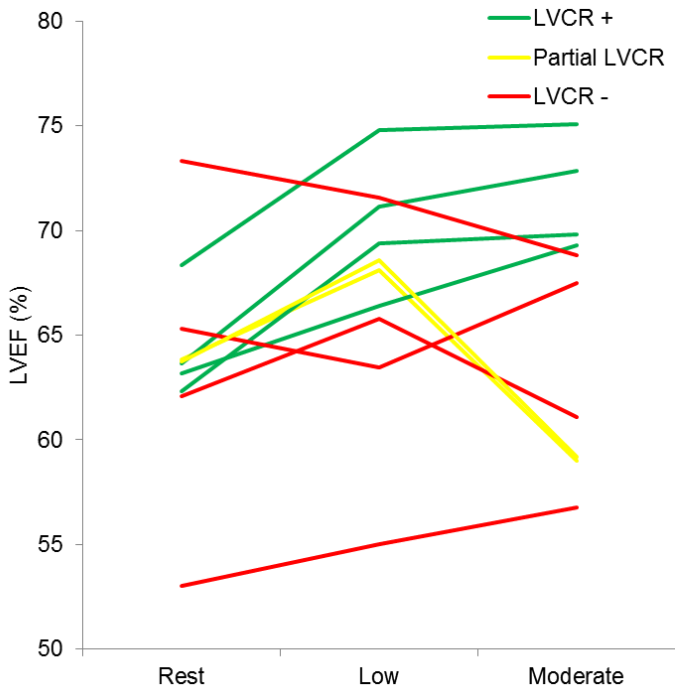


Figure 3-2 Line graph depicting the variable left ventricular cardiac reserve (LVCR) between primary MR patients during supine Ex-CMR.

4 patients had the presence of LVCR with augmentation of LVEF≥4% (LVCR +, green), 2 a partial response with initial augmentation of LVEF ≥4% then deterioration in LVEF (partial LVCR, yellow) and 4 had an absence of LVCR (LVCR - , red). Abbreviations: Ex-CMR, Exercise Cardiovascular magnetic resonance; LVEF, Left ventricular ejection fraction; MR, mitral regurgitation.

3.5.4.2 Right ventricular indices

From rest, to low and moderate exercise, RVEDVi remained unchanged (86±16ml/m^2 , 87±15ml/m^2 and 87±12ml/m^2 respectively, p=1), whilst RVESVi showed a non-statistically significant decreasing trend (38±8.0ml/m^2, 34±5.0ml/m^2 and 32±6.5ml/m^2 respectively, p=0.122) resulting in a significant increase in RVSVi (48±11ml/m^2, 53±14ml/m^2 and 55±11ml/m^2 respectively, p=0.027) and RVEF (55±5.4% vs 60±6.0% at low and 63±6.6% respectively, p=0.001).

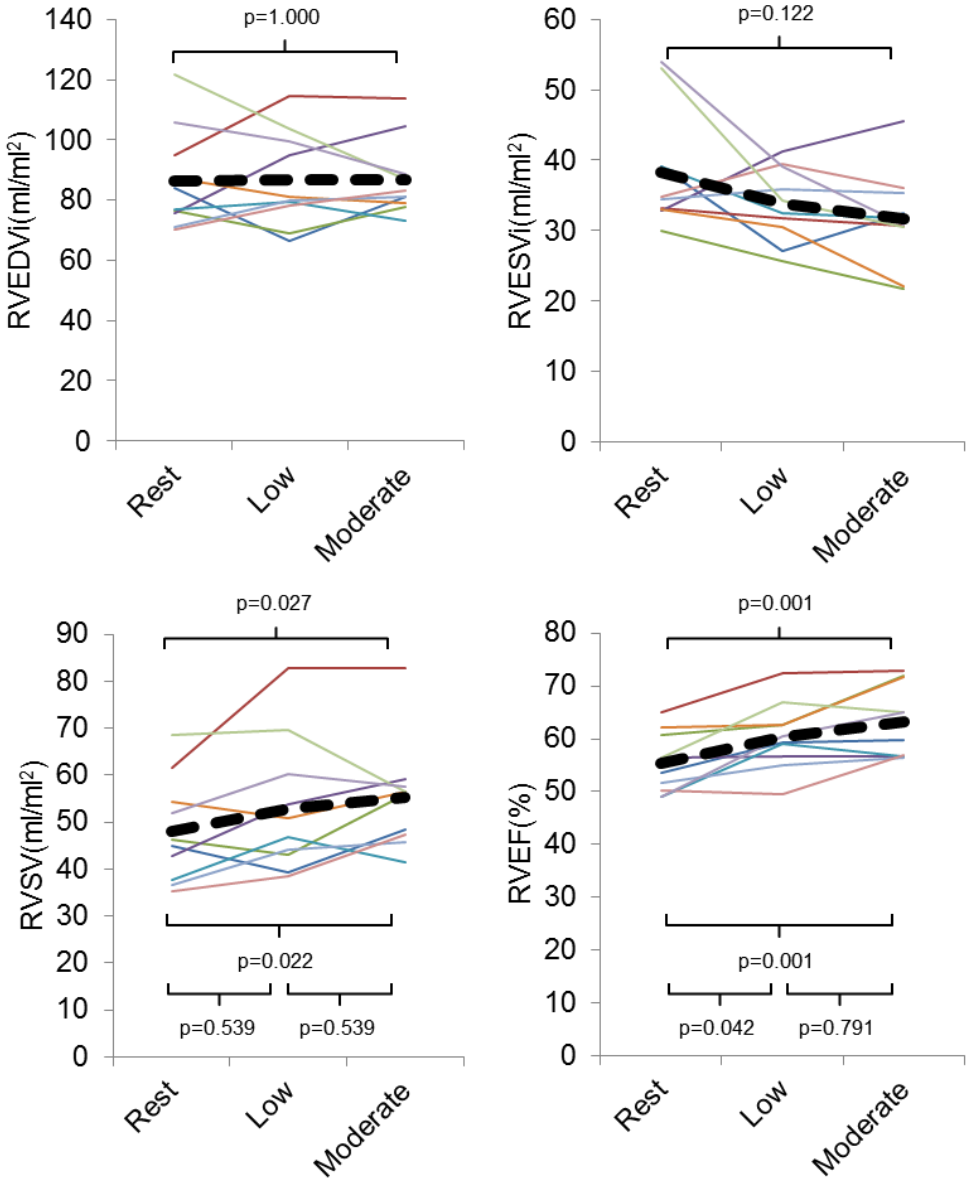


Figure 3-3 Changes in right ventricular indices during supine Ex-CMR.

RVEDVi (upper-left), RVESVi (upper right), RVSVi (lower left) and RVEF (lower-right) during supine Ex-CMR. Mean group values depicted by the dashed black line. Statistical comparison across all exercise stages presented (top of graph), which if significant then intergroup comparisons (rest vs low, low vs moderate and rest vs moderate exercise intensities) are presented (bottom of graph). Abbreviations: EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; Ex-CMR, Exercise Cardiovascular magnetic resonance; i, indexed to body surface area; RV, right ventricular; SV, stroke volume.

3.5.4.3 Mitral regurgitant volume/fraction

During Ex-CMR, from rest to low and moderate exercise, CMR quantitated MR showed a significant decrease in MR-Rvol (56±25ml to 52±23ml and 42±24ml respectively, p=0.032) and MR-RF (40±14% to 36±11% and 30±15% respectively, p=0.006). On Bonferroni post-test analysis, the differences in MR-RF were significant from rest to moderate exercise (p=0.035), but not significant for MR-Rvol differences between the exercise stages (Table 3-2) (Figure 3-4).

3.5.4.4 Aortic flow and effective forward ejection fraction

Despite no significant change in LV dimensions or LVEF during Ex-CMR, indexed aortic stroke volume increased from 41±8.3ml/m^2/cardiac cycle at rest to 47±8.3ml/m^2/cardiac cycle at low and 47±6.5ml/m^2/cardiac cycle at moderate exercise intensities (p=0.025). This was likely driven by the above described reductions in quantitated MR and allowed a significant increase in effective forward LVEF from 38±9.3% to 43±9.3% and 46±11% at rest, low and moderate exercise respectively (p=0.004) (Figure 3-4).

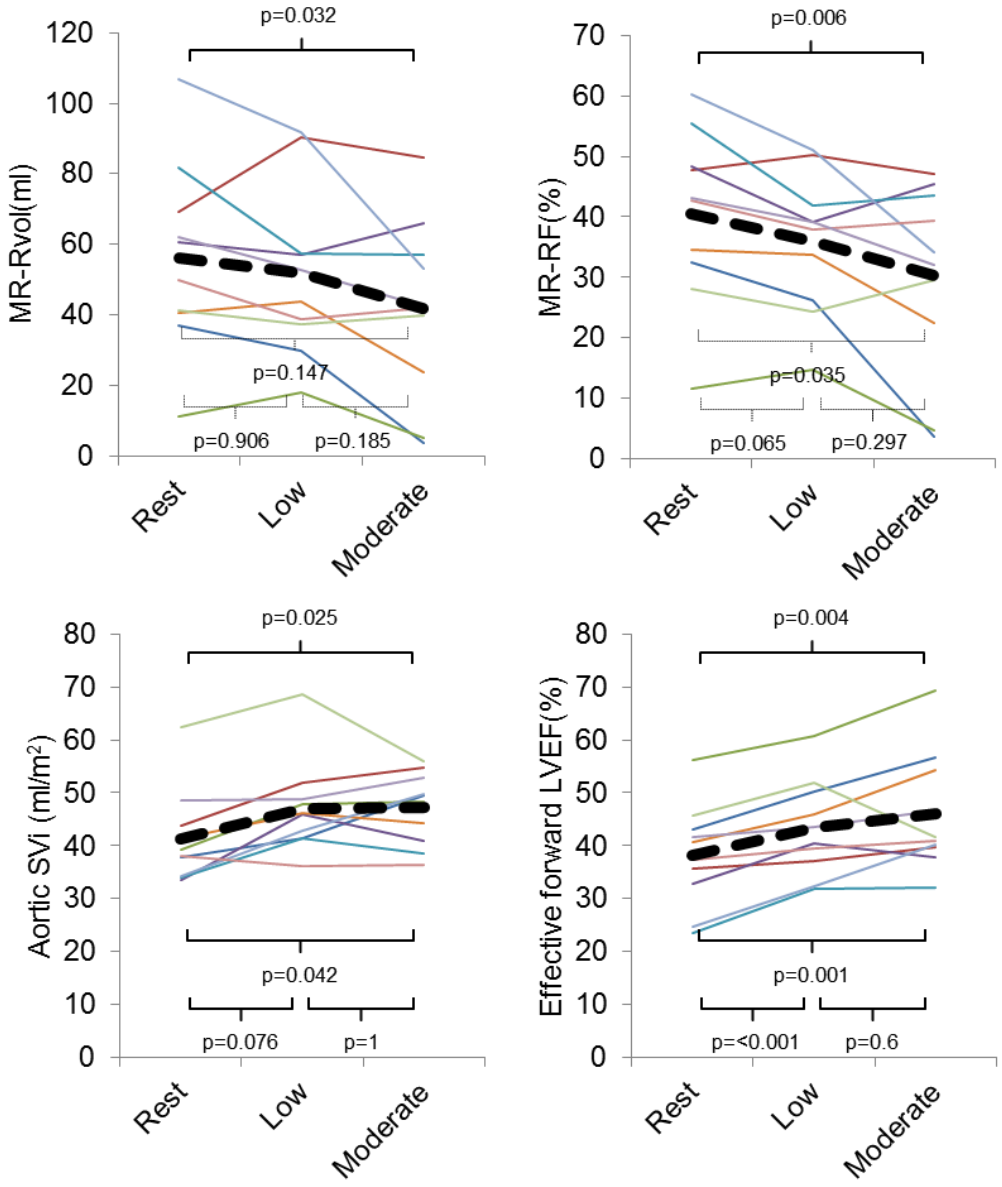


Figure 3-4 Changes in quantitated mitral regurgitation, aortic stroke volume and effective forward LVEF during supine Ex-CMR

MR-Rvol (upper-left), MR-RF (upper right), aortic SVi (lower left) and effective forward LVEF (lower-right) during supine Ex-CMR. Mean group values depicted by dashed black line. Statistical comparison across all exercise stages presented (top of graph), which if significant then intergroup comparisons (rest vs low, low vs moderate and rest vs moderate exercise intensities) are presented (bottom of graph). Abbreviations: i, indexed to body surface area; LVEF, left ventricular ejection fraction; Ex-CMR, Exercise Cardiovascular magnetic resonance; MR-Rvol, mitral regurgitant volume; MR-RF, mitral regurgitant fraction; SV, stroke volume.

Table 3-2 The haemodynamic, biventricular and mitral regurgitation indices at rest and during supine Ex-CMR

	Rest	Low intensity exercise	Moderate intensity exercise	p-values			
				All groups	Rest vs Low	Low vs Mod	Rest vs Mod
HRR % Of HR_{max}	N/A	30-39%	40-59%				
HR achieved (bpm)	61±10	98±6	115±6	<0.001	<0.001	<0.001	<0.001
Systolic BP (mmHg)	128±10	145±16	163±27	0.001	0.014	0.228	0.008
Diastolic BP (mmHg)	78±9	81±15	80±9	0.665			
Borg RPE	6±0	9.5±1.6	14.8±1.2	<0.001	<0.001	<0.001	<0.001
Cycle resistance (W)	0	51±16	82±10	<0.001	0.025	0.025	<0.001
LVEDV (ml)	210±41	209±37	199±36	0.116			
LVEDVi (ml/m^2)	112±23	111±21	107±22	0.185			
LVESV (ml)	77±23	68±19	69±21	0.15			
LVESVi (ml/m^2)	41±12	36±9.8	37±11	0.055			
LVSV (ml)	133±22	140±24	131±23	0.156			
LVSVi (ml/m^2)	71±14	75±15	70±15	0.179			
LVEF (%)	64±4.9	67±5.1	66±6.1	0.075			
Aortic SV (ml)	77±12	88±13	89±13	0.005	0.006	1	0.052
Aortic SVi (ml/m^2)	41±8.3	47±8.3	47±6.5	0.025	0.076	1	0.042
Effective Forward LVEF (%)	38±9.3	43±9.3	46±11	0.004	<0.001	0.6	0.001
MR-Rvol (ml)	56±25	52±23	42±24	0.032	0.906	0.185	0.147
MR-RF (%)	40±14	36±11	30±15	0.006	0.065	0.297	0.035

RVEDV (ml)	162±21	162±19	163±21	0.971			
RVEDVi (ml/m^2)	86±16	87±15	87±12	1			
RVESV (ml)	72±11	63±8.3	60±13	0.090			
RVESVi (ml/m^2)	38±8.0	34±5.0	32±6.5	0.122			
RVSV (ml)	90±16	99±20	104±18	0.034	0.29	0.944	0.076
RVSVi (ml/m^2)	48±11	53±14	55±11	0.027	0.539	0.539	0.022
RVEF (%)	55±5.4	60±6.0	63±6.6	0.001	0.042	0.791	0.001

Abbreviations: BP, blood pressure; BPM, beats per minute; CO, cardiac output; CI, cardiac index; EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; Ex-CMR, Exercise Cardiovascular magnetic resonance; HR, heart rate; HRR, heart rate reserve; i, Indexed to body surface area; LV, left ventricle; MR-RF, mitral regurgitant fraction; MR-Rvol, mitral regurgitant volume; RPE, rate of perceived exertion; RV, right ventricle; SV, stroke volume; W, Watts.

3.5.5 Intra/Inter-observer reproducibility

Reproducibility of cardiac parameters assessed by coefficient of variance of intra-observer and inter-observer measurements are presented in Table 3-3.

Intra-observer reproducibility of cardiac sequences assessed at rest and during exercise by CV were excellent (CV<10%) with exception of good intra-observer reproducibility of RVESV (CV 12.38%) and RVSV (CV 10.96%) at low and RVESV (CV 10.28%), MR-Rvol (CV 12.17%) and MR-RF (CV 10.62%) at moderate exercise intensities.

Inter-observer reproducibility assessed by CV of cardiac parameters were similarly excellent (CV<10%), with the exception of good inter-observer variability in RVESV (CV 10.22%) and MR-Rvol (CV 10.63%) at rest, LVESV (CV 10.70%), RVESV (CV 17.06%) and MR-Rvol (CV 10.38%) during low intensity exercise and RVESV (CV 16.68%), MR-Rvol (CV 16.74%) and MR-RF (CV 15.23%) during moderate intensity exercise.

Table 3-3 Reproducibility of cardiac indices by supine Ex-CMR in MR patients

Exercise stage	Cardiac Parameter	Co-efficient of Variance	
		Intra-observer	Inter-observer
Rest	LVEDV	1.56	2.13
	LVESV	3.83	6.17
	LVSV	1.9	3.49
	LVEF	2.08	3.25
	RVEDV	4.59	3.03
	RVESV	7.3	10.22
	RVSV	7.17	6.8
	RVEF	4.8	7.08
	Aortic stroke volume	1.57	2.46
	Effective forward LVEF	1.64	3.24
	Mitral regurgitant volume	5.05	10.63
	Mitral regurgitant fraction	3.75	8.26
Low	LVEDV	2.09	4.65
	LVESV	4.85	10.7
	LVSV	2.52	3.33
	LVEF	1.69	3.34
	RVEDV	6.36	8.36
	RVESV	12.38	17.06
	RVSV	10.96	9.93
	RVEF	7.18	9.14
	Aortic stroke volume	2.27	3.57
	Effective forward LVEF	1.68	3.96
	Mitral regurgitant volume	5.98	10.38
	Mitral regurgitant fraction	4.44	7.92
Moderate	LVEDV	2.3	3.79
	LVESV	5.05	9.06
	LVSV	2.95	3.18
	LVEF	2.18	3.19
	RVEDV	5.01	4.72
	RVESV	10.28	16.68
	RVSV	6.06	8.32
	RVEF	5.57	8.31
	Aortic stroke volume	3.05	4.08
	Effective forward LVEF	2.24	5.6
	Mitral regurgitant volume	12.17	16.74
	Mitral regurgitant fraction	10.62	15.23

Abbreviations: EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; Ex-CMR, Exercise Cardiovascular magnetic resonance; LV, left ventricle; RV, right ventricle; SV, stroke volume.

3.6 Discussion

This is the first study to perform biventricular volume/function and quantitative MR assessment during continuous supine Ex-CMR in patients with primary MR. The study has 5 important findings: 1, biventricular volume/function and quantitated MR assessment during continuous moderate supine Ex-CMR is feasible with the use of C-SENSE sequences; 2, the study demonstrates good/excellent intra/inter-observer reproducibility of biventricular indices and MR quantification; 3, the Ex-CMR protocol uses attainable equipment, sequences and software, reducing barriers to clinical utility; 4, in asymptomatic patients with at least moderate primary MR on TTE, effective forward LVEF is augmented by a decrease in MR during exercise and 5, the study agrees with prior exercise-TTE studies in demonstrating variable LVCR (85, 86, 91) and dynamic changes in MR (88) during exercise between asymptomatic primary MR patients.

3.6.1 Response to supine Ex-CMR

In our group of primary MR patients there was no significant change in biventricular dimensions or global LVEF with increasing exercise, but significant increases in RVEF and reductions in MR-RF during exercise, which resulted in an increase in effective forward LVEF.

3.6.1.1 Changes in LV volumes/function

Prior exercise TTE studies demonstrate variable changes in LV volumes/dimensions with exercise. Numerous exercise TTE studies utilising upright exercise with post stress imaging demonstrate a decrease in LVEDV/dimensions during exercise (85, 91, 327, 328), whilst exercise TTE studies using semi-supine exercise demonstrate a more variable response with Magne *et al* showing decreases in LVEDV (88) and Suzuki *et al* increases in LVEDVi with exercise (90). In keeping with prior studies investigating MR patients during fully supine exercise (93, 329), our study demonstrated no significant change in LV dimensions during exercise. Chew *et al* performed supine Ex-CMR to moderate

exercise intensity in 5 primary MR patients, showing no change in indexed LV volumes (93) and Lavie *et al* performed radionuclide angiography during supine exercise in 11 severe MR patients, also showing no change in indexed LV volumes (329). These findings may be attributable to greater venous return/preload at rest and during exercise in the supine (with legs elevated in a supine ergometer/bicycle) than upright positions (330), which may theoretically maintain an unchanged LVEDV at higher levels of exercise compared to upright exercise, during which LVEDV appears to decrease in primary MR patients (85, 88, 91, 327, 328) .

LV contractility can vary between MR patients during exercise. Indeed, our study demonstrated non-statistically significant increases in LVEF during supine Ex-CMR, whilst Chew *et al* found significant increases in LVEF (58±4% at rest to 67±3% at moderate exercise, p=0.04), (93). As discussed in chapter 1.1.3.4.1, the change in LVEF during exercise can vary between patients with primary MR, with patients having an augmentation of LVEF <4% during exercise-TTE being defined as having an absence of LVCR. Exercise-TTE studies demonstrate LVCR as an independent predictor of outcomes between groups of primary MR patients, despite statistically comparable resting MR severity and indexed left ventricular dimensions/volumes and LVEF (85, 86). Due to the variable LVCR response between primary MR patients, Magne *et al* demonstrated no significant augmentation of LVEF in their overall cohort during semi-supine exercise TTE, as 54 (47%) patients had LVCR, whilst 61 (53%) an absence of LVCR. The study recruited a similar cohort of patients to ours: asymptomatic patients with least moderate primary MR on TTE (as per ASE criteria) and preserved LVEF. Therefore the differential findings of LVEF between our cohort and that of Chew *et al*, is not un-surprising and likely explained by differing LVCR between groups. Indeed, 4 patients in our cohort failed to augment their LVEF ≥4% at any stage, whilst 2 had an initial augmentation followed by a reduction in LVEF during moderate intensity Ex-CMR (Figure 3-2).

3.6.1.2 Changes in RV volumes/function

Exercise changes in RV dimensions in primary MR patients have been minimally investigated, with the majority of prior exercise studies instead focused on changes in RV function (87, 331, 332). Only Chew *et al* has published the changes in RV volumes, also using supine Ex-CMR and demonstrated similar findings to ours. Both studies showed no change in RVEDVi during exercise. We showed a non-significant trend of reducing RVESVi with significant increases in RVSVi and RVEF, whilst Chew *et al* showed a significant decrease in RVESVi and non-significant increases in RVSVi and RVEF (93). Importantly, RV systolic function can differ between primary MR patients and has prognostic significance. Kusunose *et al* demonstrated using exercise-TTE that exercise TAPSE is an independent predictor of surgery free survival (87). Similar findings have also previously been demonstrated in an exercise radionuclide angiography study by Borer *et al*, where exercise RVEF was the best predictor of outcomes in asymptomatic severe MR patients with normal resting biventricular function, even over changes in exercise LVEF (332). The prognostic importance of exercise RVEF augmentation is not surprising, given changes in RVEF during exercise inversely correlate with changes in pulmonary pressures (87, 331, 332), rises in which during exercise are an independent predictor of adverse outcomes in patients with at least moderate primary MR with no/mild symptoms (NYHA≤II) (89, 90). Therefore, similar to LVCR being variable between primary MR patients, exercise changes in RVEF can also differ, with prognostic implications. As such, variable changes of exercise RVEF between studies with small numbers of patients is not unexpected.

3.6.1.3 Changes in quantitated MR and effective forward LVEF

MR can be dynamic during exercise. In secondary (functional/ischaemic) MR, numerous studies have investigated the dynamic changes in quantified MR during exercise TTE (36, 333-337), with patients demonstrating a dynamic increase in MR having poorer exercise capacity (337) and poorer outcomes (334, 335). In comparison, fewer studies have quantified the dynamic change in primary MR during exercise (86, 88, 92, 327). Our cohort demonstrated variable dynamic

changes in MR-Rvol during supine Ex-CMR (Figure 3-4). This is in keeping with prior exercise-TTE studies quantifying changes in primary MR (88, 327). Leung *et al* investigated 40 patients with at least moderate degenerative MR with exercise-TTE, demonstrating an increase in MR-Rvol in 32% and decrease in MR-Rvol in 68% of patients (327). Assessing our cohort by this metric, from rest to moderate exercise, 20% demonstrated an increase in MR-Rvol and 80% a decrease in MR-Rvol. Magne *et al* investigated 68 patients with at least moderate degenerative MR with rest and exercise TTE. 10% of patients were excluded due to suboptimal images during exercise, preventing accurate MR quantification. Of the remaining 61 patients, 32% demonstrated a dynamic increase in MR-Rvol (≥+15ml), 42% remained relatively unchanged, and 26% a dynamic decrease in MR-Rvol (≥-15ml). The study found that patients with a dynamic increase in MR-Rvol ≥15ml had a worse symptom free survival (88). Assessing our cohort by the same metric, 10% had a dynamic increase in MR-Rvol (≥+15ml), 40% remained relatively unchanged and 50% showed a dynamic decrease in MR-Rvol (≥-15ml). Therefore our study agrees with the prior exercise TTE studies, as regards the variable dynamic response that can occur between primary MR patients. Additionally, as discussed in section 1.1.3.3.3, MR severity is often overestimated by TTE compared with CMR during resting imaging (59, 63, 64, 71-73); the same may be true during exercise. Therefore theoretically, during Ex-CMR patients in whom MR doesn't decrease may demonstrate a poorer prognosis, likely progressing along a spectrum, with those whose MR increases demonstrating the worse outcomes. Further research across a broad range of MR severities and symptom states is required to assess this hypothesis.

In our cohort, reductions in MR during exercise allowed an increase in effective forward LVEF. Previously, effective forward LVEF has been demonstrated to be a predictor of LVEF post-surgical intervention (325), but changes during exercise have not been investigated. Given the measurement accounts for changes in LV dimensions, function and MR during exercise it could theoretically provide useful prognostic information. Additionally, as presented in Table 3-3 the measurement is highly reproducible during supine Ex-CMR and therefore warrants further assessment in prognostic studies.

Although Ex-CMR studies quantifying changes in MR have not been previously performed, our findings of reductions in valvular regurgitation with increasing exercise intensity mirror that of prior Ex-CMR studies in patients with pulmonary valve disease (285, 291). Lurz et al investigated pulmonary stenosis and pulmonary regurgitation patients with Ex-CMR pre and post PPVI, demonstrating a reduction in PR occurred in both groups during exercise. Pre-PPVI, both groups were unable to augment RVSV with exercise but maintained effective forward RVSV by reductions in PR with exercise. After PPVI, RVSV increased in both groups with exercise; however there was no significant improvement in the augmentation of effective forward RVSV during exercise in the PR group. This was attributed the significant reduction in PR pre-PPVI during exercise, due to this, the study concluded that exercise augmentations in RVSV post PPVI were mostly due to reductions in afterload rather than regurgitation (291). Therefore, Lurz et al demonstrated, similar to our study, that reductions in valvular regurgitation during exercise can facilitate an increase in effective forward flow.

3.6.2 Reproducibility

The study demonstrated that biventricular and quantitated MR assessment during supine Ex-CMR is highly reproducible with excellent reproducibility (CV<10%) of biventricular volumes and function during moderate exercise, with the exception of RVESV, which were good (CV 10-20%). However, as MR quantification by the LVSV-AoSV method is reliant on 3 measurements (LVEDV, LVESV and total aortic forward flow), a decrease in reproducibility occurred with increasing exercise. However, we still demonstrated good intra and inter-observer reproducibility at moderate exercise intensity (CV 10-20%). Interestingly, effective forward LVEF, which as discussed accounts for changes in LV volumes, function and MR showed excellent intra and inter-observer reproducibility at all stages (CV<6%). This is because it is not reliant on LVESV measurements, which are less reproducible. Therefore effective forward LVEF may be a useful assessment for future supine Ex-CMR studies.

3.6.3 Clinical implications

The rationale for use of exercise cardiac imaging in asymptomatic MR patients is to help determine which patients may benefit from early surgery. The aim is to find the optimal timing at which the MR is significant and deteriorating but has not yet resulted in such significant cardiac remodelling to cause increased peri-operative risk or adverse long term outcomes. As discussed in section 1.1.4, current guidelines advise intervention in asymptomatic patients once LV dilatation or dysfunction develop or after the onset of AF or if resting PASP is >50mmHg in the context of a valve with high probability of a durable repair (1, 39). However, once LV dilatation/systolic dysfunction develops, a patient's prognosis is often already adversely affected (338). The use of exercise imaging to tease out which patients with normal resting LV size and function are likely to deteriorate could therefore of significant use. International guidelines recognise the potential benefit of exercise echocardiography, however there are no surgical indications in the guidelines that currently utilise exercise TTE due to these 'not been sufficiently well defined to be included in current recommendations' (1). This is likely a result of a deemed insufficiency of current evidence and potentially issues around suboptimal reproducibility and inability to acquire diagnostic images in a sufficient proportion of MR patients (92), as discussed in section 1.1.3.4.1. Therefore a more robust exercise methodology may be required. As discussed, resting CMR is the reference standard in biventricular assessment (51, 52) and CMR MR quantification provides superior reproducibility and prognostic ability in in primary MR compared to TTE (63, 64). As demonstrated in exercise-TTE, LVCR, RV function (TAPSE), and dynamic changes in MR are independent predictors of outcomes in patients with primary MR (85-88, 91). Therefore the ability to assess biventricular function and quantitate MR during supine Ex-CMR is clinically appealing. This study has demonstrated the feasibility of accurate biventricular volumes, function and quantitated MR assessment during supine Ex-CMR, using vendor provided sequences, a commercially available ergometer and standard analysis software. These features make it more attainable and potentially more clinically viable than alternative free-breathing supine Ex-CMR methods that utilise the un-gated real-time method, which require specialist sequences and software

and prolonged analysis time (198, 268). Using supine Ex-CMR, in comparison to exercise-TTE, there are no limitations from acoustic windows, Doppler alignment issues or geometric assumptions, when quantifying MR using the LVSV-AoSV method. Indeed, in the research setting Magne *et al* had to exclude 10% of patients (88), as accurate MR quantification with exercise-TTE was not feasible and in the real world setting, accurate MR quantification with exercise-TTE was only feasible in 43% of patients with mitral valve prolapse (92). Where-as all patients successfully completed our supine Ex-CMR protocol with all images acquirable and analysable with good/excellent intra/inter-observer reproducibility. This protocol now needs using in a larger cohort of primary MR patients who are followed up for adverse outcomes to allow assessment of its prognostic ability. If demonstrating good prognostic ability, given MR-CPET is feasible (253), the current protocol could theoretically be adapted to be performed in tandem, therefore potentially creating an even more comprehensive assessment for borderline cases of primary MR.

Excitingly, the measurement of effective forward LVEF demonstrated excellent reproducibility at all exercise stages in our study. As discussed in section 3.2, the measurement has demonstrated prognostic utility in prior resting CMR studies (325). Given effective forward LVEF represents the ‘true’ forward flow and takes into account changes in both LVEF and MR, it may prove to be a useful single indices for use in resting and Ex-CMR. Clearly further CMR and Ex-CMR studies are needed to assess whether the measurement provides additional prognostic insight over other indices. If so, the use of a single reproducible measurement, which accounts for two significant cardiac determinants of outcomes in MR patients (MR severity and LVEF), could greatly increase the utility of both CMR and Ex-CMR in the clinical assessment of MR patients. Especially given, as discussed in section 1.1.3.1, current resting TTE assessment of MR is reliant on an integrated assessment using multiple measurements (40) and is therefore dependent on subjective analysis/combination of the various measurements to define severity.

Finally, although this study focussed on primary MR patients, it should theoretically allow accurate biventricular assessment and valve flow assessment in other

aetiologies of MR, aortic valve disease and, by reintroducing pulmonary PCMR sequences validated in Chapter 2, right heart valve or congenital heart diseases.

3.6.4 Limitations

The limitations in this study revolve around its small sample size and strict recruitment criteria, which could limit generalisability, but as will be discussed may not limit clinical application. Similar to the study in Chapter 2 and prior Ex-CMR studies, the MR scanner bore can restrict knee clearance making supine Ex-CMR difficult in tall patients. Importantly, height was not an exclusion criteria and our tallest volunteer in this study was 182cm. Our cohorts mean BMI was on the border between healthy and overweight (24.8±3.3 kg/m^2), with 50% a healthy weight (BMI 20-25) and 50% overweight (BMI 25-30), and therefore our protocol has not been validated in obese patients, who may find supine Ex-CMR more difficult, but supine Ex-CMR has previously been demonstrated feasible in obese patients in a prior study (249). All patients in our study were asymptomatic (NYHA I) and in sinus rhythm. Symptomatic patients may not tolerate supine Ex-CMR as well, which could result in increased physical and respiratory motion, artefacts from which could make image acquisition and analysis more difficult. The presence of AF may make retrospective ECG gating during supine-Ex-CMR more difficult, which could prolong image acquisition/exercise time and may impact on image acquisition and reproducibility. However, the rationale for developing this protocol for use in primary MR patients is to help guide management in borderline cases, where patients do not have clinical or echocardiographic indications for surgery/intervention at rest. Given the development of symptoms or new onset of AF, in the context of TTE defined severe MR, is an indication for surgical intervention (37, 39), then the lack of demonstrating feasibility in symptomatic patients, or those in AF may not significantly limit its clinical use.

Cycle duration in the study was longer than ideal for clinical use (mean 20 minutes 6 seconds), as patients were imaged at two exercise intensities, but well tolerated by all patients with none needing to terminate early. As demonstrated in Figure 3-2, this gives the benefit of demonstrating patients with an initial favourable exercise response prior to deterioration. Such findings would be missed by only imaging at

rest and one exercise stage. Future studies are required to assess if such features place patients in a different prognostic group. However, if such studies do not demonstrate any additional benefit to imaging at low intensity exercise, then removal of this stage would reduce overall cycling time, making the protocol more clinically viable.

Patients in our study were exercised to moderate exercise intensity with a mean HR of 115bpm and not until exhaustion/peak stress. However, our achieved HR at moderate fully supine exercise was only slightly lower than semi-supine exercise-TTE studies by Magne *et al*, which were sufficient to demonstrate prognostic significance of LVCR at a mean exercise HR of 127bpm (86) and dynamic increases in MR at a mean exercise of HR 125±13bpm (88). Indeed, the LVCR study by Magne *et al* acquired the images to assess LVCR at heart rates between 90-110bpm (86). Given CMR is a more accurate assessment of biventricular volumes/function and MR quantification, the data acquired during moderate supine Ex-CMR may theoretically be sufficient to provide beneficial prognostic information.

As per SCMR guidelines (339), MR quantification in the study was performed by assessing aortic flow from PCMR sequences planned at the sino-tubular junction. This has the potential to overestimate MR severity compared with aortic flow assessed at the valve level (340). However CMR studies demonstrate MR quantification by this the technique is highly reproducible (62, 63, 71), provides superior prognostic assessment compared with TTE (63, 64) and as such is the recommended site and method of MR quantification by CMR (339). Indeed TTE MR quantification can overestimate MR severity compared with the LVSV-AoSV technique (59, 63, 64, 71-73). As a result, as our recruitment was reliant on baseline TTE, our cohorts baseline MR severity on CMR assessment was more variable than the planned initial recruitment, with one patient that had moderate MR on TTE, having mild MR on baseline CMR assessment.

Finally, the sample size in this study is small, initial plans for this thesis was to include 20 patients in this study; unfortunately recruitment was restricted by onset of the COVID-19 pandemic. Fortunately sufficient patients were recruited before the onset of the pandemic to demonstrate feasibility and reproducibility in this

patient cohort. However, the small sample size prevents in-depth analysis to assess if resting CMR can predict exercise changes in biventricular volumes/function and quantitated MR. Importantly, recruitment in this study is ongoing to overcome this issue and assess the protocols prognostic ability.

3.7 Conclusion

Assessment of biventricular function and MR quantification during continuous supine Ex-CMR to moderate intensity is feasible and reproducible. The Ex-CMR protocol utilises vendor provided C-SENSE sequences, a commercially available ergometer and standard analysis software, increasing widespread attainability, potentially making it more clinically viable. Further research is now warranted to assess the prognostic ability of the Ex-CMR protocol in primary MR patients and assess feasibility in other valve diseases and congenital heart disease.

Chapter 4

Cardiac reverse remodelling for primary mitral regurgitation: mitral valve replacement vs. mitral valve repair

4.1 Abstract

Background

When feasible, mitral valve repair (MVr) is recommended over mitral valve replacement (MVR), to treat primary mitral regurgitation (MR), based upon historic outcome studies and reverse remodelling studies using transthoracic echocardiography (TTE). Cardiovascular magnetic resonance (CMR) offers reference standard biventricular volume and function assessment with superior MR quantification reproducibility compared to TTE. In patients with primary MR we investigated cardiac reverse remodelling and quantitated changes in MR post-MVr vs MVR with chordal preservation, using sequential CMR for comprehensive assessment.

Methods

83 patients with at least moderate-severe MR on TTE were prospectively recruited. CMR imaging and 6-minute walk tests (6MWT) were performed at baseline and 6 months after mitral surgery or watchful waiting (control group). CMR protocol included: cines for left ventricular (LV) and right ventricular (RV) volumes, aortic/pulmonary through-plane phase contrast imaging. MR was quantitated indirectly by the LV-aortic stroke volume method.

Results

72 patients completed follow-up (Controls=20, MVr=30 and MVR=22). Baseline cardiac indices, co-morbidities and surgical risk scores were comparable between

surgical groups. Baseline biventricular volumes/function were also comparable between groups, except for greater right ventricular ejection fraction (RVEF) in controls than MVr and MVR groups (54±8% vs 46±6.6% and 46±9.4% respectively, p=0.002). Baseline MR regurgitant fraction (MR-RF) was lower in controls than MVr and MVR groups (39±13% vs 50±10% and 52±13% respectively, p=0.001). At 6 months, compared with controls, MVr and MVR groups demonstrated improved 6MWT distances (+0.1±55m vs +57±54m and +64±76m respectively, p=0.002) and decreased indexed left-ventricular end-diastolic volumes (-1.3±12ml/m^2 vs -29±21 ml/m^2 and -37±22 ml/m^2 respectively, p<0.001), indexed left atrial volumes (+1.2±19ml/m^2 vs -27±30 ml/m^2 and -39±26 ml/m^2 respectively, p<0.001) and MR-RF (+0.4±7.0% vs -29±11 and -40±14 respectively, p<0.001). Biventricular reverse remodelling was comparable between surgical groups, except poorer RVEF post-MVr compared with controls (47±6.1% vs 53±8.0% respectively, p=0.01). MVR resulted in lower residual MR-RF than MVr (12±8.0% vs 21±11% respectively, p=0.022).

Conclusion

In primary MR, MVR with chordal preservation may offer comparable cardiac reverse remodelling benefits at 6-months compared to MVr. Larger, multicentre CMR studies are required, which if confirmed, might then have implications for future surgical practice.

4.2 Introduction

Mitral regurgitation is the commonest valve disease in the US and second commonest indication for valve surgery in Europe (94, 341). Current guidelines recommend MVr over MVR whenever feasible (1, 39), as observational studies comparing techniques typically demonstrate worse early and long-term mortality post MVR (120, 121). However, numerous studies supporting this recommendation pre-date the routine use of chordal preservation techniques with MVR (116-120), which improves cardiac reverse remodelling post MVR (112-115, 342). Indeed, cardiac reverse remodelling between MVr/MVR is comparable when chordal preservation is used (126, 127) and inferior post MVR when not (117, 118). In a broad range of cardiac disease, cardiac reverse remodelling is associated with a more favourable prognosis (128, 129), therefore lack of chordal preservation in comparative studies may result in significant bias. Importantly, MVR is more frequently performed in patients with more complex mitral valve disease, advanced age, reduced LVEF and worse NYHA functional class, than patients referred for MVr (123). Unfortunately, a randomised trial comparing MVr/MVR in primary MR has not been performed and studies using propensity matching in an attempt to overcome intrinsic bias present conflicting results (123, 124). In ischaemic MR, a randomised trial demonstrated no significant difference in survival or left ventricular reverse remodelling at 2-years between MVr vs MVR with chordal preservation, but greater recurrent MR in the MVr group, resulting in more heart failure related adverse events and hospital admissions (125). In primary MR, recurrent MR post MVr is not uncommon, with mod-severe MR reported in 13-17% in longitudinal studies (135, 136) and associated with adverse LV remodelling and late mortality (343). MVr typically results in equivalent (120, 123, 124) or more reoperations than MVR (130), however, the reoperation end-point may not account for all recurrent significant MR if patients are not keen, or deemed too high risk for repeat surgery.

Accurate assessment of mitral regurgitation is paramount to guide the need for surgical intervention and provide appropriate outcome comparisons between MVr/MVR. CMR is the reference standard for biventricular volume and functional assessment (52, 53) and compared to TTE, CMR MR quantification has been shown to have superior reproducibility (59, 60, 62, 63) and prognostication in

primary MR (63, 64). Importantly, MR severity assessment by CMR and TTE can be discordant, especially in cases of late-systolic, eccentric or multiple regurgitant jets (63). However, CMR defined MR severity correlates stronger with clinical outcomes than TTE (63, 64), suggesting it is more accurate. TTE can also overestimate MR severity in comparison to CMR (59, 63, 64, 71-73). Indeed, Uretsky *et al* demonstrated in two studies that only 32-37% of those who underwent surgical correction due to echocardiogram-defined severe MR, had severe MR by CMR criteria (59, 72). Ultimately randomised trials comparing MVr vs MVR and/or comparing outcomes post-echocardiogram vs CMR-guided surgical intervention could guide future clinical decision making. Prior to this, rigorous hypothesis-generating observational data will be required; this study aimed to assess differences in cardiac reverse remodelling and residual MR (assessed by CMR) following surgical MVr and MVR with chordal preservation for primary MR, compared to a matched control group (moderate-severe MR patients on a watchful waiting pathway). A control group has been included in this study to allow a comprehensive comparison between the surgical groups and controls.

4.3 Methods

4.3.1 Study design

This single-centre prospective observational cohort study recruited patients between February 2016 and February 2020 with primary MR from the cardiology/cardiac surgery out-patient departments at Leeds Teaching Hospitals NHS Trust, Leeds, UK. Inclusion criteria: moderate-severe or severe primary MR on echocardiography, aged >18 years, suitable/accepted for surgical intervention, with capacity to provide written informed consent. Exclusion criteria: Secondary (functional/ischaemic/atrial) MR, contraindications to CMR, significant (≥ moderate severity) aortic valve disease, uncontrolled AF >120bpm, NYHA functional Class IV, terminal illness, haemodynamic instability, renal failure with an estimated glomerular filtration rate of <30ml/min/1.73m^2, weight >130kg, pregnancy or breast feeding, or inability to lie flat for 60 minutes. A watchful waiting control group was

included to allow for a comprehensive comparison with surgical groups and to allow assessment of cardiac remodelling that occurs in these groups.

At least moderate-severe MR was defined by a combined assessment of qualitative and quantitative echocardiographic measures as per ASE guidelines: vena contracta >0.7cm^2, PISA radius >0.8cm, EROA >0.3cm^2, MR-Rvol >45ml/beat, MR-RF >40% (40). Surgical intervention (timing and technique) was decided by a multidisciplinary heart team, as per international guidance (1, 37), that were independent from the study. Patients underwent standard pre-operative assessment for MV intervention including TOE and left+/- right heart catheterisation. Baseline clinical and demographic data were recorded for all patients. CMR imaging and 6-minute walk tests (6MWT) were performed at baseline and 6-months post-surgery (MVR or MVr) or post watchful waiting (control group). 6MWT was performed as per American Thoracic Society (ATS) guidelines (344). Written informed consent was provided by all patients. The study was approved by the local research ethics committee (Yorkshire & The Humber-South Yorkshire 15/YH/0503) and complied with the Declaration of Helsinki (see appendix).

4.3.2 CMR imaging

Baseline and 6-month follow-up CMR were performed (1.5T Philips Ingenia, Best, Netherlands). CMR protocol involved: 1. Survey images, 2. LV short axis multi-slice, multi-phase cine imaging bSSFP sequence (TR 3msec, TE 1.6msec, flip angle 60°, SENSE factor 2, 10mm thickness, 0mm gap, in-plane spatial resolution 1.2 x 1.2mm, 30 phases, matrix 192x131, voxel size 1.88x1.88mm, typical FOV 340mm), 3. 4-chamber and 2-chamber cine imaging to calculate LA volume and right atrial (RA) area, 4. Dedicated transaxial RV multi-slice, multi-phase bSSFP cine imaging (TR 2.8msec, TE 1.41msec, flip angle 60°, SENSE factor 1.8, 8mm thickness, 0mm gap, in-plane spatial resolution 1.88 x 1.88mm, 20 phases, matrix 192x143, voxel size 1.88x1.88mm, typical FOV 360mm).5. Two orthogonal LVOT and RVOT views to plan aortic and pulmonary PCMR imaging respectively, 6. Through-plane aortic and pulmonary PCMR, planned at the aortic sino-tubular

junction, orthogonal to the aorta, to assess aortic flow and approximately 1cm superior to the pulmonary valve, orthogonal to the main pulmonary artery to assess pulmonary flow. VENC was set to 150cm/s as standard and increased for repeat imaging if aliasing occurred. All PCMR sequences were planned with region of interest in the iso-centre of the MRI scanner to reduce background phase-offset errors (74, 75). Other PCMR parameters: typical FOV 350x280mm, TR 5.1msec, TE 3.2msec, flip angle 15°, temporal resolution 28msec, number of signal averages 1, SENSE factor 2, TFE factor 3, TFE acquisition duration 30.8ms, slice thickness 8mm, 30 phases, phase percentage 100%, in-plane spatial resolution 2.5×2.5mm, matrix 140x112, Cartesian sampling, and typical acquisition times, 12-15 seconds for breath-held sequences. In patients with AF, two acquisitions of aortic/pulmonary PCMR imaging with the same parameters were obtained and the results averaged to account for heart rate variation.

4.3.3 CMR analysis

Images were analysed using commercially available software (cvi42, Circle Cardiovascular Imaging, Calgary, AB, Canada). Biventricular endocardial contours were manually traced; the papillary muscles and trabeculations were considered part of the ventricular blood pool and volumes calculated by summation of disks (319). Maximal left atrial volume was calculated using the bi-plane area-length method from 2 and 4-chamber cine images during ventricular systole, corresponding to the last cine image before opening of the mitral valve (345). Maximal right atrial area was measured, inclusive of the right atrial appendage, from 4-chamber cine images during ventricular systole, corresponding to last cine image before opening of the tricuspid valve (345, 346). Aortic and pulmonary flows were assessed by manually contouring the vessel in every phase. As per prior studies (62-64) and SCMR recommendations (69), mitral and tricuspid regurgitation were quantified indirectly using the following formulas respectively: Mitral regurgitant volume (MR-Rvol) = left ventricular stroke volume – aortic stroke volume and tricuspid regurgitant volume (TR-Rvol) = right ventricular stroke volume – pulmonary stroke volume.

4.3.4 Surgical technique

Surgical procedures were performed by one of four experienced cardiac surgeons in our centre, under general anaesthesia using a standard cardiopulmonary bypass technique via a 7-10 cm midline sternotomy incision and mild systemic hypothermia (30-34°C). Intra-operative TOE was utilised. Systemic heparinisation aorto-bicaval cannulation was performed. LA incision was made to expose and inspect the pathological mitral valve. All MVr were performed using Gore-Tex chordae sutures and supported by a Carpentier-Edwards Physio II annuloplasty ring (typical size 29-34mm). MVR were performed using the St Jude mechanical valve, Edwards Perimount Magna bioprosthetic valve or St Jude Epic™ Mitral stented tissue valve with Linx™ AC technology (typical size 27-33mm). At least partial chordal preservation was performed with MVR as routine practice. The type of prosthetic valve, preservation technique and suture placement technique were at the discretion of the surgeon. Protamine was administered prior to wound closure with stainless steel myowires over mediastinal drains. Mechanical MVR patients were treated with life-long anticoagulation (Vitamin K antagonist-warfarin) post procedure. In selected cases AF was ablated with radiofrequency and coinciding left atrial appendage ligation performed.

4.3.5 Statistical analysis

Data were analysed using SPSS version 26 (IBM Corp.). All continuous data were assessed for normality using Shapiro-Wilk test. Baseline, follow-up/residual and the changes from baseline to follow up variables were compared between the three groups (control/MVr/MVR). Continuous variables are expressed as mean±SD and categorical variables expressed as frequencies and percentages. Continuous data was assessed between all groups with ANOVA with Bonferroni post-hoc analysis for normally distributed variables and Kruskal-Wallis with Bonferroni post-hoc analysis for non-normally distributed variables. Categorical data was compared by Fisher's Exact test, which was preferred to the Chi squared test as this test is less valid in small groups and/or those with low frequency of variables ($n<5$) (326, 347). If a significant difference was found between all groups, Fisher's Exact tests were

performed between each group to assess inter-group differences. $p<0.05$ was considered statistically significant.

4.4 Results

Eighty-three patients were recruited and scanned at baseline. By group, 34 patients underwent MVr (4 dropped out: 1 death, 3 declined follow up: 1 developed motor neuron disease and 2 declined due to COVID-19 pandemic); 24 underwent MVR (2 dropped out: 2 deaths); 25 controls were observed with watchful waiting (5 dropped out: 3 deaths, 2 declined follow up: 1 due to claustrophobia and 1 developed lung cancer). This resulted in 72 patients with paired CMR scans at 6 months: 30 MVr, 22 MVR (14 metallic, 8 bio-prosthetic valves) and 20 controls (Figure 4-1).

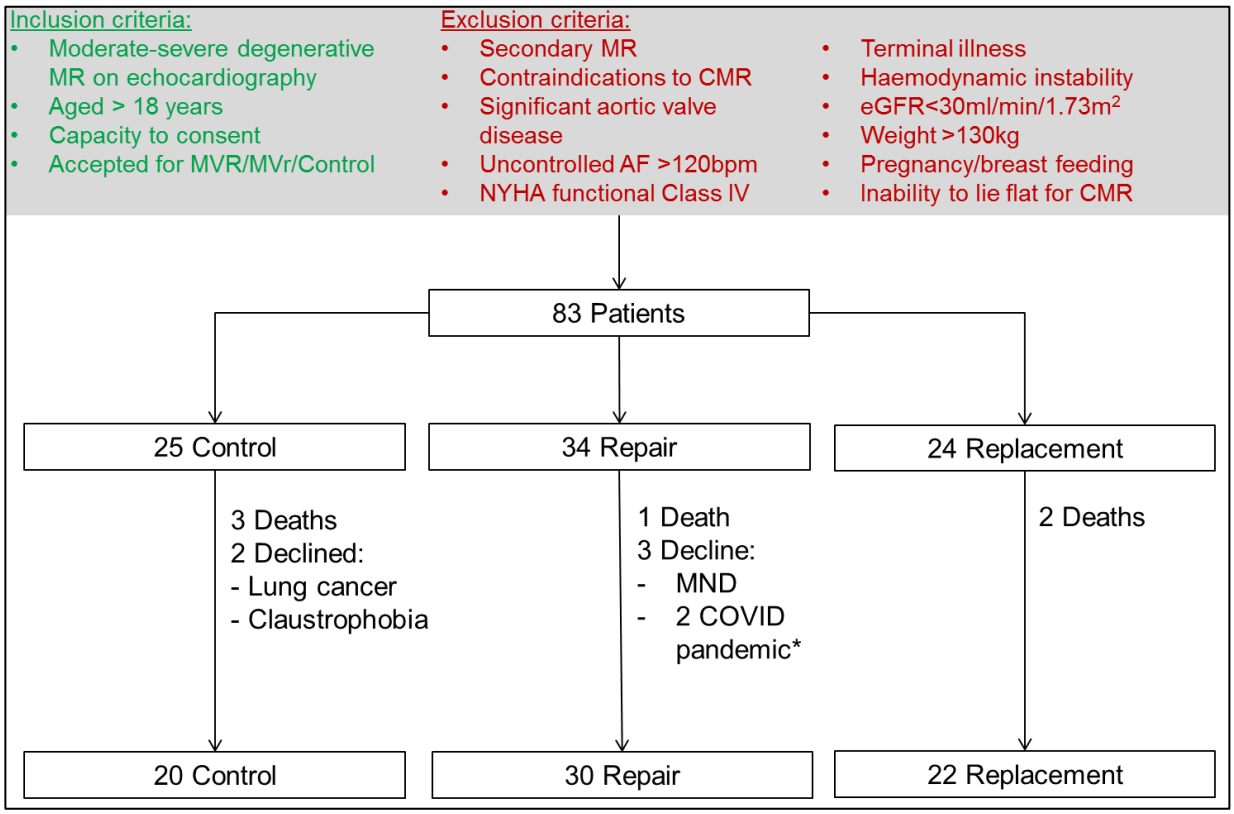


Figure 4-1 A figure to demonstrate the studies inclusion/exclusion criteria and patient flow

*2 patients decline follow up imaging due to the COVID-19 pandemic.
Abbreviations: AF, atrial fibrillation; CMR, cardiovascular magnetic resonance; eGFR, estimated glomerular filtration rate; MND, motor neuron disease; MR, mitral regurgitation; MVr; mitral valve repair; MVR, mitral valve replacement; NYHA, New York heart association.

4.4.1 Baseline patient characteristics

Baseline characteristics of the groups are presented in Table 4-1. There was no difference in age or sex between the groups. The underlying leaflet(s) affected differed between surgical groups (p=0.014), with a greater proportion of PMVL disease in the MVr group and AMVL disease in the MVR group. The proportion of patients with flail leaflets was comparable between all groups (p=0.703). NYHA functional class was lower in the control, than the MVr and MVR groups at 1.3±0.6 vs 1.9±0.7 and 2.2±0.7 respectively (p=0.001). There were no statistically significant differences in surgical risk scores (Log Euro/Log EuroII/ STS Mortality/morbidity) between groups. The MVr and MVR groups had a greater proportion of patients with AF than the control group (p=0.021) at 16 (53%) and 13 (59%) vs 4 (20%) respectively. There were otherwise no statistically significant differences in comorbidities between groups at baseline.

Table 4-1 Baseline patients characteristics

	Control (n=20)	Repair (n=30)	Replace (n=22)	P-values			
				All groups	Control vs Repair	Control vs Replace	Repair vs Replace
Male	11 (55%)	24 (80%)	16 (73%)	0.186			
Age (years)	64±18	67±11	66±10	0.935			
Duration to follow-up (days)*	233±8	188±27	194±25	0.001	0.001	0.008	1
BMI (kg/m^2)	24.1±3.3	26.2±3.8	25.3±5.0	0.275			
Systolic BP (mm/Hg)	125±25	125±15	125±13	1			
Diastolic BP (mm/Hg)	73±16	77±13	77±10	0.54			
Heart rate (bpm)	71±10	72±15	72±13	0.885			
6MWT distance (m)	393±118	365±103	358±79	0.485			
NYHA functional class:							
I	15 (75%)	8 (27%)	4 (18%)	0.001	0.003	0.001	0.256
II	4 (20%)	16 (53%)	9 (41%)				
III	1 (5%)	6 (20%)	9 (41%)				
IV	0	0	0				
Aetiology:							
Leaflet affected: PMVL	12 (60%)	26 (87%)	12 (54%)	0.027	0.149	0.332	0.014
Leaflet affected: AMVL	1 (5%)	1 (3%)	5 (23%)				
Leaflet affected: Bi-leaflet	7 (35%)	3 (10%)	5 (23%)				
Presence of flail leaflet	4 (20%)	8 (27%)	7 (32%)	0.703			

Surgical risk scores:							
Log Euro	5.6±4.7	4.7±3.5	3.7±2.4	0.736			
Log Euro II	1.5±1.4	1.4±1.0	1.6±1.2	0.523			
STS mortality	1.5±1.6	1.2±1.2	1.9±1.6	0.076			
STS mortality/morbidity	11.8±7.1	9.5±4.9	13.2±5.9	0.053			
Comorbidities:							
Smoking History	7 (35%)	14 (47%)	8 (36%)	0.713			
Diabetes mellitus	2 (10%)	1 (3%)	1 (5%)	0.679			
Hypertension	4 (20%)	11 (37%)	6 (27%)	0.486			
Atrial fibrillation	4 (20%)	16 (53%)	13 (59%)	0.021	0.022	0.014	0.781
Prior myocardial infarction	1 (5%)	0	1 (5%)	0.507			
Prior PCI	2 (10%)	0	1 (5%)	0.183			
Prior Stroke	1 (5%)	0	0	0.278			
Prior TIA	1 (5%)	1 (3%)	1 (5%)	1			
COPD	2 (10%)	1 (3%)	2 (9%)	0.599			
Chronic Kidney Disease	1 (5%)	0	1 (5%)	0.507			
Haemoglobin (g/L)	137±11	143±10	140±14	0.15			
Creatinine (umol/L)	79±14	81±18	88±20	0.244			

* Duration of time until repeat CMR imaging after either surgical intervention or baseline CMR in control group. Abbreviations: 6MWT, 6-minute walk test; AMVL, anterior mitral valve leaflet; BMI, body mass index; BP, blood pressure; BPM, beats per minute; BSA, body surface area; COPD, chronic obstructive pulmonary disease; NYHA, New York heart association; PCI, percutaneous coronary intervention; PMVL; posterior mitral valve leaflet; TIA, transient ischaemic attack.

4.4.2 Baseline CMR cardiac parameters

Baseline cardiac parameters as assessed by CMR are presented in Table 4-2. There were no statistically significant differences in baseline biventricular volumes between the groups, although lower RVEF in the MVR and MVr groups than controls at 46±6.6% and 46±9.4% vs 54±8.0% respectively (p=0.002). As per Table 4-2, there were no baseline differences in CMR quantified AR, PR or tricuspid regurgitation (TR) between the groups. The control group had lower baseline quantitated MR than the MVr and MVR groups with an MR-Rvol of 49±25ml vs 66±26ml and 71±29ml (p=0.002) and MR-RF of 39±13% vs 50±10% and 52±13% respectively (p=0.001). There were no statistically significant differences on baseline CMR between both surgical groups. Therefore, there were no significant baseline differences between the two surgical groups, except differences in leaflet involvement

Table 4-2 Baseline CMR cardiac parameters

	Groups			P-values			
	Control (n=20)	Repair (n=30)	Replace (n=22)	All groups	Control vs Repair	Control vs replace	Repair vs Replace
LVEDVi (ml/m^2)	118±25	124±31	131±27	0.332			
LVESVi (ml/m^2)	50±14	56±20	61±19	0.153			
LVSVi (ml/m^2)	69±14	68±16	70±13	0.85			
LVEF (%)	59±5	55±7.8	54±8.1	0.173			
LVMi (g/m^2)	53±13	62±14	63±18	0.063			
LA volume indexed (ml/m^2)	85±23	94±31	107±36	0.063			
AR Rvol (ml)	3.6±3.8	4.2±2.1	3.4±2.4	0.111			
AR RF (%)	4.8±3.9	6.8±3.7	5.8±4.1	0.106			
MR Rvol (ml)	49±25	66±26	71±29	0.002	0.012	0.004	1
MR RF (%)	39±13	50±10	52±13	0.001	0.002	0.001	1
RVEDVi (ml/m^2)	93±24	94±20	98±17	0.429			
RVESVi (ml/m^2)	43±12	51±14	54±16	0.034	0.113	0.041	1
RVSVi (ml/m^2)	52±16	43±10	44±9.3	0.033	0.041	0.102	1
RVEF (%)	54±8	46±6.6	46±9.4	0.002	0.004	0.005	1
PR Rvol (ml)	2.3±2.2	3.4±3.3	2.5±1.6	0.421			
PR RF (%)	2.9±2.2	5.2±5.5	3.9±3.0	0.191			
TR Rvol (ml)	12±16	16±15	15±13	0.385			
TR RF (%)	13±14	19±18	17±15	0.353			
RAAi (cm^2/m^2)	14±3	15±3.8	15±4.3	0.319			

Abbreviations: AR, aortic regurgitation; EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; i, indexed to body surface area; LA, left atrial; LV, left ventricular; LVM, left ventricular mass; MR, mitral regurgitation; PR, pulmonary regurgitation; RAA, right atrial area; RF, regurgitant fraction; Rvol, regurgitant volume; RV, right ventricular; SV, stroke volume; TR, tricuspid regurgitation.

4.4.3 Surgical variables

The operation variables are compared between the two surgical groups in Table 4-3. Thirty patients underwent MVr and twenty-two patients underwent MVR (Prosthesis: metallic =14, tissue=8). MVr and MVR groups were comparable in terms of concomitant coronary artery bypass grafting (2 vs 2 respectively, p=1.00), tricuspid valve repair (5 vs 2 respectively, p=0.685) and AF ablations (1 vs 2 respectively, p=0.567). There were no statistically significant differences in the cardiopulmonary bypass time (CBT) and cross clamp time (CCT) between the MVr and MVR groups at 124±26min vs 132±47min (p=0.837) and 96±28min vs 94±41min (p=0.333) respectively. After dividing the MVR group into those with direct MVR (n=16) and those with MVR after an attempted repair (MVRar) (n=6), the MVRar group had longer surgical procedure times than direct MVR and MVr groups, with CBT of 190±32min vs 111±31min and 124±26min (p=0.001) and CCT of 146±39min vs 74±19min and 96±28min (p=0.001) respectively. On sub-group analysis, direct MVR patients had equivalent bypass (p=0.216) but shorter cross clamp times (p=0.046) than the MVr group.

Table 4-3 Operation variable comparisons between surgical groups

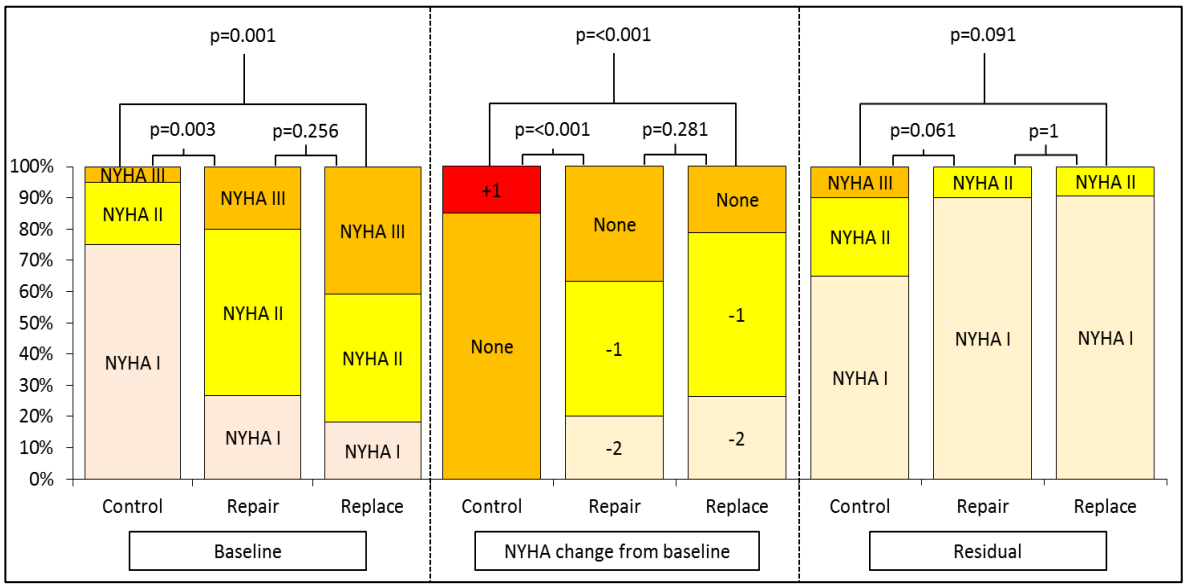
Surgical variable	Repair (n=30)	Replace (8 tissue, 14 metallic)	P-Value(s)			
CABG	2 (7%)	2 (9%)	1			
AF ablation	1 (3%)	2 (9%)	0.567			
TV repair	5 (17%)	2 (9%)	0.685			
Bypass duration (min)	124±26*	132±47	0.837			
Crossclamp time (min)	96±28*	94±41	0.333			
		Attempted repair?				
	Repair (n=30)	No (n=16)	Yes (n=6)	All groups	MVr vs MVR	MVr vs MVRar	MVR vs MVRar
Bypass duration (min)	124±26*	111±31	190±32	0.001	0.216	<0.001	0.012
Crossclamp time (min)	96±28*	74±19	146±39	0.001	0.046	0.071	0.001

Surgical variables between groups and differences between groups when mitral valve replacement was group divided into those that received direct replacement and those who had replacement after an attempted repair (MVRar). * Surgical duration unavailable for 1 patient in repair group. Abbreviations: AF, atrial fibrillation; CABG, coronary artery bypass grafting; MVr, mitral valve repair; MVR, mitral valve replacement; MVRar, mitral valve replacement after attempted repair.

4.4.4 Functional outcomes

Changes between the groups from baseline to follow up are presented in Table 4-4. Differences in NYHA functional class at baseline, follow up and change are shown in Figure 4-2. At follow up, compared with controls, the MVr and MVR groups demonstrated improved 6MWT distances (+0.1±55m vs +57±54m and +64±76m respectively, p=0.002) and NYHA functional class (p<0.001) with no statistically significant differences between both surgical groups in either outcome. After these changes, there were no statistically significant differences between all groups in residual 6MWT distances or NYHA functional class on follow up assessment (Table 4-5).

Figure 4-2 Direct inter-group comparisons of baseline, delta change and residual NYHA functional class between control, repair and replacement groups



Inter-group statistical comparisons displayed (Control vs repair, control vs replace, repair vs replace). Abbreviations: NYHA, New York Heart Association functional class.

4.4.5 Cardiac reverse remodelling

Changes to cardiac indices between baseline and follow up CMR are shown in Table 4-4 and the resultant residual cardiac indices are compared between groups in Table 4-5. Compared with controls, MVr and MVR resulted in comparable significant reductions in LVEDVi (-1.3±12ml/m^2 vs -29±21ml/m^2 and -37±22ml/m^2 respectively, p<0.001), LVEF (+0.4±3.9% vs -8.7±8.9% and -8.8±9.0% respectively, p<0.001) and indexed left atrial volumes (+1.2±19ml/m^2 vs -27±30ml/m^2 and -39±26ml/m^2 respectively, p<0.001) (Table 4-4), resulting in lower LVEDVi (94±28ml/m^2 and 94±25ml/m^2 vs 117±28ml/m^2 respectively, p=0.005) and LVEF (47±9.2% and 46±8.1% vs 59±5.0% respectively, p<0.001) at 6-month follow-up CMR in the MVr and MVR groups compared with controls (Table 4-5). There were no statistically significant differences between surgical groups in the changes to, or, residual left ventricular volumes/function or left atrial volume. There were no statistically significant differences between groups in terms of change to right ventricular volumes/function and right atrial areas, resulting in comparable residual right heart indices, except for lower residual RVEF in the MVr group compared with the controls (47±6.1% vs 53±8.0% respectively, p=0.01). There was no statistically significant difference in residual RVEF between MVr and MVR groups (47±6.1% vs 50±5.7% respectively p=0.224).

4.4.6 Changes in quantitated valve regurgitation

Both surgical groups demonstrated a significant reduction in and lower residual MR-Rvol and MR-RF compared with the control group (p<0.001) (Table 4-4 & Table 4-5). MVR resulted in a superior reduction in MR-RF (-40±14% vs -29±11%, p=0.002), resulting in lower 6-month residual MR-RF compared with the MVr group (12±8.0% vs 21±11% respectively, p=0.022). There were no significant differences between all three groups in changes to or residual quantitated aortic, pulmonary or tricuspid regurgitation.

Table 4-4 Change in functional, haemodynamic and cardiac parameters from baseline to follow up assessment

	Groups			P-values			
	Control (n=20)	Repair (n=30)	Replace (n=22)	All groups	Control vs Repair	Control vs replace	Repair vs Replace
Systolic BP(mmHg)	-0.2±21	+0.8±11	+0.1±12	0.952			
Diastolic BP(mmHg)	+0.5±14	+2.8±10	+0.1±9.2	0.510			
Heart rate (bpm)	-3.0±10	+3.1±21	-1.8±12	0.359			
6MWT distance (m)	+0.1±55	+57±54	+64±76	0.002	0.007	0.005	1
NYHA class	0.15±0.4	-0.8±0.7	-1.1±0.7	<0.001	<0.001	<0.001	0.281
LVEDVi (ml/m^2)	-1.3±12	-29±21	-37±22	<0.001	<0.001	<0.001	0.584
LVESVi (ml/m^2)	-1.7±7.4	-4.0±16	-8.3±18	0.360			
LVSVi (ml/m^2)	-0.1±8.4	-25±15	-28±13	<0.001	<0.001	<0.001	1
LVEF (%)	+0.4±3.9	-8.7±8.9	-8.8±9.0	<0.001	<0.001	0.001	1
LVMi (g/m^2)	+0.3±4.3	-3.8±10	-3.7±11	0.256			
LA volume indexed (ml/m^2)	+1.2±19	-27±30	-39±26	<0.001	0.002	<0.001	0.545
AR Rvol (ml)	+0.3±1.4	-0.3±2.4	-0.2±2.1	0.117			
AR RF (%)	+0.8±2.4	-0.8±3.4	-1.1±4.1	0.161			
MR Rvol (ml)	-0.1±12	-47±21	-62±27	<0.001	<0.001	<0.001	0.064
MR RF (%)	+0.4±7.0	-29±11	-40±14	<0.001	<0.001	<0.001	0.002
RVEDVi (ml/m^2)	-0.9±5.5	-5.0±16	-7.1±20	0.436			
RVESVi (ml/m^2)	+0.6±5.5	-3.5±14	-9.1±17	0.051			
RVSVi (ml/m^2)	-3.3±9.0	-1.5±11	+1.9±10	0.487			

RVEF (%)	-0.8±4.0	+1.0±9.5	+4.9±7.9	0.067	
PR Rvol (ml)	-0.4±1.5	+0.3±2.0	-0.1±1.7	0.224	
PR RF (%)	-0.2±1.7	-0.2±3.4	-0.9±3.3	0.424	
TR Rvol (ml)	+0.5±21	-5.1±17	-2.9±13	0.493	
TR RF (%)	+2.1±21	-6.6±20	-4.5±14	0.614	
RAAi (cm^2/m^2)	0.0±2.5	0.0±2.9	-1.1±3.9	0.568	

Abbreviations: 6MWT, 6-minute walk test; AR, aortic regurgitation; BP, blood pressure; BPM, beats per minute; EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; i, indexed to body surface area; LA, left atrial; LV, left ventricular; LVM, left ventricular mass; MR, mitral regurgitation; NYHA, New York heart association functional class; PR, pulmonary regurgitation; RAA, right atrial area; RF, regurgitant fraction; Rvol, regurgitant volume; RV, right ventricular; SV, stroke volume; TR, tricuspid regurgitation.

Table 4-5 Residual functional, haemodynamic and cardiac parameters on follow up assessment

	Groups			P-values			
	Control (n=20)	Repair (n=30)	Replace (n=22)	All groups	Control vs Repair	Control vs replace	Repair vs Replace
Systolic BP (mmHg)	125±14	126±12	125±15	0.975			
Diastolic BP (mmHg)	73±10	80±11	77±11	0.134			
Heart rate (bpm)	68±11	75±15	71±8.3	0.141			
6MWT distance (m)	393±109	422±82	422±111	0.586			
NYHA (mean)	1.45±0.7	1.1±0.3	1.1±0.3	0.087			
LVEDVi (ml/m^2)	117±28	94±28	94±25	0.005	0.011	0.016	1
LVESVi (ml/m^2)	48±15	52±23	52±20	0.863			
LVSVi (ml/m^2)	69±15	42±9.3	42±8.6	<0.001	<0.001	<0.001	1
LVEF (%)	59±5	47±9.2	46±8.1	<0.001	<0.001	<0.001	1
LVMi (g/m^2)	54±11	59±15	60±17	0.307			
LA volume indexed (ml/m^2)	86±28	67±37	69±28	0.115			
AR Rvol (ml)	3.9±4.1	3.9±3.4	3.2±2.2	0.912			
AR RF (%)	5.6±5.1	6.0±4.3	4.6±3.2	0.588			
MR Rvol (ml)	49±23	19±13	9.5±7.0	<0.001	<0.001	<0.001	0.088
MR RF (%)	39±13	21±11	12±8.0	<0.001	0.001	<0.001	0.022
RVEDVi (ml/m^2)	92±24	89±18	91±20	0.875			
RVESVi (ml/m^2)	44±14	48±13	45±12	0.459			

RVSVi (ml/m^2)	49±15	42±8.6	46±11	0.093			
RVEF (%)	53±8	47±6.1	50±5.7	0.011	0.01	0.698	0.224
PR Rvol (ml)	1.8±1.6	3.7±3.5	2.3±2.2	0.022	0.086	1.000	0.145
PR RF (%)	2.4±2.0	5.0±4.1	3.0±2.5	0.045	0.058	1.000	0.062
TR Rvol (ml)	13±17	11±10	12±9.0	0.628			
TR RF (%)	15±20	13±11	13±8.8	0.809			
RAAi (cm^2/m^2)	14±3	15±3.6	14±3.6	0.511			

Abbreviations: 6MWT, 6-minute walk test; AR, aortic regurgitation; BP, blood pressure; BPM, beats per minute; EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; i, indexed to body surface area; LA, left atrial; LV, left ventricular; LVM, left ventricular mass; MR, mitral regurgitation; NYHA, New York heart association functional class; PR, pulmonary regurgitation; RAA, right atrial area; RF, regurgitant fraction; Rvol, regurgitant volume; RV, right ventricular; SV, stroke volume; TR, tricuspid regurgitation.

4.5 Discussion

To our knowledge, this is the first study to compare cardiac reverse remodelling and quantify residual MR between MVr and MVR using the reference standard (CMR), with a longitudinal control group for comparison. Importantly, at baseline the study had naturally well matched surgical groups, with no statistically significant differences in cardiac parameters and co-morbidities. The study has three important findings: Firstly, MVr and MVR resulted in comparable LV reverse remodelling; secondly, RVEF was worse post-MVr vs controls than post-MVR and thirdly, MVR resulted in a greater reduction in MR and lower residual MR than MVr.

As described CMR is the reference standard for biventricular assessment (52, 53) and arguably more accurate at assessing MR severity than TTE (59, 63, 64, 72). Indeed, disparity in accuracy may increase post operatively, as TTE assessment of MR severity is difficult due to acoustic shadow artefacts (348-350) occurring secondary to mitral annular rings (implanted during MVr or as a component of a bio-prosthetic valve) or more profoundly with metallic prosthesis (349, 350). Indeed, the ASE/ESC state no single parameter can reliably quantitate prosthetic MR via TTE, advising combined TTE and TOE assessment (348), potentially reducing the accuracy of TTE studies comparing residual MR between surgical groups (MVr vs MVR). Using CMR, prosthesis-related distortions of the magnetic field can create the potential for volume and flow miscalculation. However, this can be mitigated with consistent LV basal slice analysis and using indirect MR quantification (LVSV-AoSV method), as aortic PCMR, planned carefully to avoid artefact, increases the distance from the prosthesis and therefore accuracy of PCMR flow assessment (351). Therefore, to date, our study may provide the most accurate comparison of cardiac reverse remodelling and residual MR between MVr/MVR for primary MR.

Patients undergoing MVR are typically older with more comorbidities than those referred for MVr. In primary MR, propensity matched studies performed to overcome these biases present conflicting results, with Gilinov *et al* demonstrating no significant difference between long term survival and freedom from re-operation

between MVr and MVR with chordal preservation (123), whilst Lazam *et al* found lower operative mortality, better long term survival and fewer valve related complications post MVr . However, Lazam *et al* specifically assessed patients with flail leaflets and the use of chordal preservation techniques with MVR was not clearly documented (124). In our study, baseline cardiac indices, surgical risk scores and co-morbidities were similar between surgical groups, potentially minimising this bias. There were differences in leaflets affected between groups, with the MVr group more typically having PMVL disease than the other groups. This is unsurprising given PMVL prolapse is more amenable to successful surgical repair (96) and international guidelines advise repair whenever feasible (1, 39), making this difficult to control for in an observational study. At baseline, compared to the watchful waiting control group, both surgical groups demonstrated worse NYHA functional class, quantitated MR, RVEF and had a greater proportion of patients in AF, demonstrating as expected that the surgical groups were at a more advanced stage on the MR severity spectrum.

Our left ventricular reverse remodelling findings demonstrate equivalency between MVr and MVR. These findings are in keeping with prior echocardiographic studies (126, 127, 352) and the only prior CMR study (325), which compared remodelling at 3 months between MVr and MVR with chordal preservation (n=28). Similar to previous studies, we demonstrated a significant decrease in LVEF post-operatively (126, 127, 353), finding no significant difference between surgical groups. Given previous concerns over poorer LVEF post MVR (117, 118), our results from a rigorous study design using CMR to assess remodelling/LVEF, comparing both surgical groups at baseline and 6-months post-surgery and against an observational control group, will hopefully act as re-assurance against this concern. As discussed in section 4.2, prior studies demonstrating poorer outcomes post MVR typically have biased baseline variables with older MVR groups with more co-morbidities (123) and/or predate the routine use of chordal preservation with MVR (116-120), with chordal preservation now known to be essential to help preserve post-operative LVEF (112-115, 342). Importantly, our study used chordal preservation with MVR and had naturally matched baseline variables between the

groups, reducing innate bias between surgical groups, and showed no difference in cardiac remodelling between MVr and MVR.

In keeping with Uretksy *et al*, who similarly assessed cardiac reverse remodelling following corrective mitral valve surgery with CMR in two studies, we found no significant change in indexed right ventricular size (EDV/ESV) post-MVr and MVR (59, 72). Both studies by Urestky *et al*, the majority of which had MVr, demonstrated no significant change between pre- and post-operative RVEF (p=0.05). Unfortunately, the studies had small numbers of MVR patients and therefore remodelling comparisons between surgical techniques were not performed. Our study demonstrated lower RVEF post-MVr vs controls (p=0.01), but no statistically significant difference between the two surgical groups (p=0.224). However, our MVr group underwent a proportionally greater number of tricuspid valve repairs than the MVR group (5 vs 2 respectively), which may have blunted the RVEF augmentation in the MVr group. There were however no statistically significant differences in the quantified tricuspid regurgitant fraction between the groups pre-operatively or at follow-up to support this. Therefore, the lower RVEF in the MVr group vs controls may be as a result of a lower reduction in and greater residual MR-RF compared with the MVR group.

MVR compared to MVr resulted in a greater reduction in MR-RF post-operatively and hence lower residual MR-RF. Whilst the absolute reduction in and residual MR-Rvol was lower for MVR vs MVr, this was not statistically significant. On explanation for this, MR-Rvol is a non-indexed measurement, and therefore more dependent on haemodynamic variables, chamber size and body surface area, whereas MR-RF takes into account the patients LV stroke volume, better accounting for these variables. As such, MR-RF has been considered a more accurate imaging biomarker of MR severity (354). Our findings of greater residual MR post-MVr are in keeping with prior echocardiographic studies (127, 133).

Our study has the benefit of using a watchful-waiting control group. This has provided three specific benefits. 1, highlight the baseline differences between patients with mod-severe primary MR on TTE that are observed or referred for surgery, specifically demonstrating greater MR and poorer RVEF in those referred

for surgery. This is an important finding, as it suggests that quantifying MR and RVEF by CMR, rather than categorising severity as per TTE, may more accurately define severity. 2, the use of a control group allowed a more comprehensive comparison than between two surgical groups alone. Specifically, without the use of a control group, the poorer RVEF post-MVr would not have been highlighted. 3, the demonstration of minimal cardiac remodelling in the control group over the 6-month period, suggests that (at least as regards cardiac remodelling) asymptomatic primary MR patients with similar characteristics/cardiac indices are unlikely to deteriorate quickly and therefore are reasonably monitored by watchful waiting with a 6-month interval between imaging. Further studies utilising CMR are required to investigate patients on watchful waiting observational management, to further define cut offs at which more intensive imaging is required and define when early intervention provides prognostic benefit.

Only one prior CMR study by Gelfand et al has compared cardiac reverse remodelling between MVr/MVR (325). The study performed sequential CMR at baseline and 3 months in 20 primary MR patients that underwent mitral valve surgery (14 MVr, 6 MVR), 14 of which had a further CMR at 27-months. They demonstrated MR reduction and cardiac reverse remodelling post-surgery with no difference in outcomes between surgical groups. With the caveat of potential differences in CMR acquisition and analysis between the Gelfand study and ours: the baseline cardiac indices in Gelfand cohort had a lower mean age (53years), LVEDVi (113m/m2), LVESVi (45ml/m2), MR-RF (40%), MR-RVol (54ml) and higher LVEF (62%) and RVEF (51%) than either of our surgical groups. Indeed baseline cardiac indices in the Gelfand cohort bear closest resemblance to our control group. Therefore the Gelfand cohort were younger, had less severe MR and cardiac remodelling at baseline, potentially suggesting intervention was performed earlier in the disease process than in our cohort. Despite this, we present similar findings of LV remodelling with reductions in LVEDVi, LVESVi and LVEF in both surgical groups. Our study acquired follow-up imaging at 6-months demonstrating reduced LVEF than pre-operatively. Interestingly, at 27-months follow-up of the Gelfand cohort, the LVEF had normalised and LV volumes had further decreased. Therefore a reduced LVEF at 6-months compared to pre-

operative values in both surgical groups in our study either suggests that cardiac reverse remodelling is incomplete with further improvement yet to occur, or that the increased LV volumes and lower LVEF pre-operatively in our cohort has resulted in poorer post-operative LVEF than compared with the Gelfand cohort. Additionally, residual MR was higher in both our surgical cohorts than the Gelfand cohort. This may also be a result of potentially earlier intervention in the Gelfand cohort, or potentially explainable by differential CMR protocols/analysis between our two studies. Further CMR studies, ideally larger and with longer follow-up are required to assess the optimal timing of surgery in the disease process for primary MR patients to improve outcomes and determine the approximate time at which reverse re-modelling post-surgical intervention is complete to assist in the design of future studies.

4.5.1 Clinical implications

Perhaps controversially, our findings of comparable cardiac reverse remodelling following MVr and MVR and lower residual MR-RF post-MVR, pose a challenge to the current recommendation of ‘repair whenever feasible’. If confirmed in larger series, they might suggest that current recommendations could be down-graded to permit direct MVR in more complex pathologies in order to reduce surgical procedural times. Given that CBT and CCT both correlate with post-operative mortality and morbidity (355, 356), relaxing the recommendations in selected cases may not adversely affect cardiac reverse remodelling and might positively impact on surgical outcomes. Given MVR is arguably more durable, with less recurrent MR (127, 133) then our results, if replicated in randomised trials could significantly impact clinical practice. However, the decision to offer a patient MVR or MVr has multiple facets. Bioprosthetic MVRs are prone to degeneration and are therefore best reserved for patients in whom it will last a lifetime (1, 109). A metallic prosthesis requires anticoagulation, coming with inherent bleeding risks and increased stroke risk if this becomes sub-therapeutic (106, 107). As such, it is understandable that a successful MVr is clinically appealing. However, our study demonstrates equivalent cardiac remodelling between the techniques and greater

MR post MVr. Therefore, in elderly patients in whom a tissue valve replacement will last a lifetime or younger patients with another indication for anticoagulation, our results suggest that an MVR may be the optimal treatment. Larger multi-centre studies will be required, using CMR to assess remodelling and quantify MR and with a longer follow-up period to assess clinical outcomes before such clinical recommendations could be made.

Beyond the scope of the comparative findings between MVr and MVR, our study also adds to several prior CMR studies (59, 63, 64, 72) demonstrating the benefit CMR can offer in the assessment and decision making in mitral regurgitation patients. Our results are controversial, potentially challenging the current accepted premise that MVr is superior to MVR. Our findings may be in part due to the use of CMR highlighting significant changes that may be otherwise missed by TTE. Most notably greater residual MR post MVr compared with MVR. As the reference standard for biventricular assessment, with MR quantification with superior reproducibility to TTE, CMR is arguably the most accurate imaging modality currently available to assess MR severity and resultant cardiac remodelling. As such, subtle changes are more easily highlighted than with TTE. Therefore our findings, when assessed alongside prior CMR studies (59, 63, 64, 72), suggest CMR should provide a greater role in the clinical assessment of primary MR patients both pre and post-surgical intervention and to accurately guide research inclusion criteria and assess outcomes. Further research utilising CMR is therefore essential to continue to optimise management of patients with mitral regurgitation.

4.5.2 Limitations

This was a single centre prospective observational study therefore larger multicentre studies are required to validate the findings. We specifically recruited patients with primary MR and those undergoing elective surgery, therefore our results may not be generalizable to those with secondary MR or undergoing emergency surgery. As a non-randomised study intrinsic baseline differences between the groups could not be controlled. However, as demonstrated in Table 4-1, there were no statistically significant differences between the surgical groups

in terms of age, sex or comorbidities. Despite differences in the underlying leaflet pathology between surgical groups there was no statistically significant difference in cardiac reverse remodelling. The group sizes are modest by comparison with prior longitudinal MVR and MVr outcome studies, however the use of CMR and its high reproducibility for volumes (51, 52) and flow quantitation (59, 60, 62, 63) means that much smaller sample sizes are required to detect a change compared to standard TTE. Baseline cardiac indices were equivalent between surgical groups, but there was a non-significant tendency towards larger bi-ventricular volumes, left atrial volumes and quantitated MR in the MVR group. A larger study may have highlighted these differences as significant, potentially making the comparative residual cardiac indices between surgical groups more impressive. Except for 2 patients who had complete chordal preservation with MVR, MVR were performed with partial chordal preservation as routine practice in our study; however, complete chordal preservation is the optimal technique (115), which may have made remodelling differences between the groups more significant in favour of MVR. Finally, our study specifically assessed cardiac reverse remodelling and functional changes after 6-months, so the study is unable to confirm that residual differences between surgical groups would result in different long term clinical outcomes.

4.6 Future directions

Our findings demonstrate the need for further research comparing MVr vs MVR with chordal preservation, specifically using CMR to assess cardiac reverse remodelling. Multiple variables are involved in the long term outcomes of patients after mitral valve surgery including the effect of the surgery itself, coinciding cardiac conditions and other non-cardiac/un-related disease processes affecting morbidity/mortality. As such, studies assessing clinical outcomes often use significantly large sample sizes to balance out confounding variables (129). Indeed, many such studies can span decades, in which time period standards and success of treatment can change (124, 130), also potentially impacting results. The assessment of cardiac remodelling closely correlates with clinical outcomes (129),

doesn't necessitate long follow up periods to assess (reducing the potential for confounding variables to impact follow up assessments) and can be assessed accurately and reproducibly by CMR. Therefore assessment of cardiac reverse remodelling can be a useful surrogate for assessing clinical outcomes (129). Indeed, theoretically it is arguable that non-cardiac processes/diseases more proportionally adversely impact a patient's symptoms, morbidity and mortality than they do the cardiac remodelling process. Therefore, ideally future comparative studies comparing MVr/MVR should assess both cardiac reverse remodelling using CMR and perform long term follow up to assess long term clinical outcomes. This approach would allow for comparison of immediate follow up effects between surgical groups and assess long term results. Ideally future studies are required to build on the work presented in this Chapter. Initially multicentre studies comparing MVr vs MVR with chordal preservation in primary MR patients, using CMR to assess remodelling and prolonged follow up to assess clinical outcomes. If results of such studies prove promising, then a randomised trial comparing MVr vs MVR, using recruitment criteria defined from the prior multi-centre studies, would be warranted and may significantly alter clinical practice.

4.7 Conclusion

In primary MR, MVR with chordal preservation may offer comparable cardiac reverse remodelling benefits at 6-months compared to MVr. Larger, multicentre CMR studies are required, which if confirmed might then have implications for future surgical practice.

Chapter 5

Assessment of cardiac reverse remodelling following percutaneous mitral valve intervention in primary mitral regurgitation: a cardiovascular magnetic resonance study

5.1 Abstract

Background

Mitral valve repair is advised, when feasible, to treat significant primary MR, however many patients are deemed too high-risk and declined surgery. Percutaneous mitral valve interventions have been developed to treat this high-risk cohort. Accurate assessment of cardiac reverse remodelling is essential to guide optimal patient selection. CMR is the reference standard for cardiac volumetric assessment and compared to TTE provides superior reproducibility in MR quantification pre and post MitraClip^{TM} insertion. Prior CMR studies have analysed cardiac reverse remodelling post MitraClip^{TM} in combined cohorts of primary and secondary MR patients. However, aetiology of MR can significantly impact outcomes. Therefore this study aimed to assess cardiac reverse remodelling and quantitate changes in MR after percutaneous intervention for primary MR using the reference standard (CMR).

Methods

11 patients with significant MR on TTE were prospectively recruited to undergo CMR imaging and 6-minute walk tests (6MWT) at baseline and 6 months post percutaneous mitral valve intervention. CMR protocol involved: left-ventricular (LV) short axis cines, transaxial right-ventricular (RV) cines, two and four chamber cines and aortic/pulmonary through-plane phase contrast imaging. MR was quantitated indirectly using LV and aortic stroke volumes.

Results

10 patients underwent MitraClip^{TM} for PMVL prolapse with 1 suffering partial clip detachment and declining follow-up and 1 patient underwent TMVI for failing mitral bio-prosthesis. From baseline to 6-month follow-up assessment: significant improvements occurred in NYHA functional class (p=0.019), 6MWT distances (205±101m to 269±64m, p=0.016) and RVEF (43±8.3% to 50±9%, p=0.035), significant reductions occurred in LVEDVi (118±23ml/m^2 to 92±28ml/m^2, p=0.001), LVESVi (59±20ml/m^2 to 47±21ml/m^2, p=0.005) and quantitated MR-Rvol (55±23ml to 23±13ml, p=0.005). There were no significant changes in LVEF, right ventricular or bi-atrial dimensions or quantitated aortic/pulmonary/tricuspid regurgitation.

Conclusion

Successful percutaneous mitral valve intervention for primary MR results in reduced MR, positive left ventricular reverse remodelling, preservation of LVEF and augmentation of RVEF, but no significant changes to right ventricular or bi-atrial dimensions at 6 months. Larger CMR studies are now required to further guide optimal patient selection and compare the varying percutaneous techniques available.

5.2 Introduction

When feasible, surgical mitral valve repair is advised as first line treatment for significant primary MR (1, 39). However, numerous symptomatic patients with severe primary MR are deemed high risk and declined surgical intervention (138). Percutaneous mitral valve interventions have developed to treat this cohort of high risk patients including the MitraClip™ procedure and TMVI. MitraClip™ has demonstrated excellent technical success resulting in acute MR reduction and low mortality and morbidity rates in treating high-risk MR patients (143), but has proven inferior to conventional mitral valve surgery in a randomised trial (144). In carefully selected patients with functional MR and reduced ejection fraction, MitraClip™ improves outcomes compared with optimal medical therapy alone (145, 147). TMVI is an effective treatment for high-risk patients with recurrent MR after prior mitral valve surgery, with proven clinical efficacy post failed bioprosthesis and failed MVr with annuloplasty ring (153-155).

Assessing cardiac reverse remodelling after mitral valve surgery/intervention is important to guide future patient selection. Multiple previous studies have assessed cardiac reverse remodelling with TTE post MitraClip™ (144, 357-360). One such study by Brouwer *et al* investigated 79 patients (81% secondary MR) with echocardiography at baseline, 1 and 6-months post MitraClip™. Reverse remodelling, no remodelling and adverse remodelling occurred in 51%, 42% and 8% of patients respectively, with a higher mortality in adverse remodelling patients compared with reverse remodelling patients (359). The study demonstrated the importance of investigating characteristics of patients likely to have reverse/adverse remodelling to guide patient selection and success of treatment. Therefore the accuracy of the image modality assessing remodelling is also extremely important. CMR is the reference standard for biventricular assessment (52, 53) and compared to TTE demonstrates superior reproducibility in MR quantification (63, 64), even post MitraClip™ (361) and arguably offers a more accurate assessment of MR severity than TTE, with TTE more prone to overestimate MR severity compared with CMR (59, 72). CMR is therefore the optimal imaging modality to assess cardiac reverse remodelling and quantitate residual MR post percutaneous intervention. Indeed, prior CMR studies assessing

reverse remodelling post percutaneous mitral valve intervention have been conducted. Krumm *et al* demonstrated reductions in LVEDV, LVESV, LV mass and LA area by CMR in 27 patients (13 primary MR, 14 secondary MR) at baseline and 3 months post MitraClip^{TM}; RV remodelling and changes in quantified MR were not assessed (362). Radunski *et al* investigated biventricular remodelling with CMR in 12 MR patients (5 primary MR, 7 secondary MR) at baseline and 6 months post MitraClip^{TM}, demonstrating reductions in LVEDVi, LVESVi but no change in LVEF, LA volumes or RV parameters; unfortunately, changes in quantified MR were not assessed (363). Lurz *et al* demonstrated an acute reduction (within 7 days) of LVEDVi and MR-RF post MitraClip^{TM} by CMR in 20 patients (5 primary MR, 15 secondary MR) and similarly demonstrated no changes in RV parameters or tricuspid regurgitant fraction (TR-RF) (364). To date, no CMR study has assessed cardiac reverse remodelling post percutaneous intervention in primary MR alone, but performed pooled analysis inclusive of primary and secondary MR. Given underlying aetiology can significantly impact outcomes post percutaneous intervention (162, 357, 360, 365), a focussed study assessing remodelling in primary MR using CMR may be beneficial to guide future patient selection. Therefore, this study aimed to use the reference standard (CMR) to assess cardiac reverse remodelling and changes in quantified MR in primary MR patients post percutaneous mitral valve intervention.

5.3 Methods

5.3.1 Study design

This single-centre prospective observational cohort study recruited patients between June 2016 and January 2020 with moderate-severe primary MR from the cardiology/cardiac surgery out-patient departments at Leeds Teaching Hospitals NHS Trust, Leeds, UK. The methodology for this study is the same as the study in Chapter 4 (described in Chapter 4.3), with identical echocardiographic criteria for defining moderate-severe MR and with the same investigations performed (CMR and 6MWT at baseline and 6-month follow-up). However, as the study involves a

different cohort of patients there are alterations to inclusion/exclusion criteria (described below).

Inclusion criteria: moderate-severe or severe primary MR on echocardiography, aged > 18 years with capacity to consent to study participation and have been accepted for percutaneous mitral valve intervention.

Exclusion criteria: Secondary (functional/ischaemic/atrial) MR, contraindications to CMR, significant (≥moderate severity) aortic valve disease, uncontrolled AF >120bpm, terminal illness, haemodynamic instability, weight >130kg, pregnancy or breast feeding, or inability to lie flat for 60 minutes.

Percutaneous intervention was decided by a multidisciplinary heart team, independent from the study, as per international guidance (1, 37) and after patients had been declined for surgical intervention. Baseline clinical and demographic data were recorded for all patients. The study was approved by the local research ethics committee (Yorkshire & The Humber- South Yorkshire 15/YH/0503) and complied with the Declaration of Helsinki (See Appendix); all patients provided written informed consent.

5.3.2 CMR imaging

The CMR imaging protocol utilised in the study is as used in the Chapter 4 study and described in chapter 4.3.2.

5.3.3 CMR analysis

The methods of CMR analysis used in this study are as per the Chapter 4 study and described in chapter 4.3.3.

5.3.4 Statistical analysis

Data were analysed using SPSS version 26 (IBM Corp.). All continuous data were assessed for normality using Shapiro-Wilk test. The difference between variables at baseline and 6-month follow-up were compared. Continuous variables are expressed as mean±SD and categorical variables expressed as frequencies and percentages. Continuous data was assessed by the paired t-test and Wilcoxon signed ranks test for normally and non-normally distributed data respectfully.

Changes in categorical data were compared by Fisher's Exact test, which was preferred to the Chi squared test due to low group numbers and small frequencies in some categorical variables (326, 347). $p<0.05$ was considered statistically significant.

5.4 Results

5.4.1 Baseline patient characteristics

After assessment against the inclusion/exclusion criteria 11 patients were recruited. 10 patients underwent percutaneous MitraClip^{TM} procedure and 1 patient underwent TMVI. 1 patient who underwent percutaneous MitraClip^{TM} suffered clip displacement resulting in device failure and declined further involvement in the study. This resulted in 10 patients (aged 82±5 years, 8-male) completing follow-up imaging after 6.7±1.4 months (9 MitraClip^{TM} & 1 TMVI), who were included for analysis. At baseline, 3 patients had NYHA II, 6 patients NYHA III and 1 patient NYHA IV symptoms (Table 5-1). The majority (90%) of patients had MR as a result of PMVL prolapse and were treated with MitraClip^{TM}. 1 patient had a failed bioprosthesis and was treated with TMVI. As expected in this cohort of patients, numerous patients had co-morbidities: diabetes (90%), hypertension (50%), AF (80%), prior MI (30%), prior stroke (10%), prior transient ischaemic attack (10%) and chronic kidney disease (50%).

5.4.2 Functional and haemodynamic outcomes

Changes in the functional and haemodynamic parameters are displayed in Table 5-1. Post percutaneous mitral valve intervention, from baseline to follow up: 6MWT distances improved significantly (205±101m to 269±64m, $p=0.016$) and NYHA functional class improved significantly ($p=0.019$) (figure 5.1). There were no significant differences between baseline and follow up in: heart rate (73±7bpm to 71±15bpm, $p=0.568$), systolic (126±15mmHg to 135±13mmHg, $p=0.333$) or diastolic (72±10mmHg to 78±8mmHg, $p=0.268$) blood pressure, haemoglobin (120±24g/L to 137±24g/L, $p=0.062$) or creatinine (113±37umol/L to 122±46umol/L, $p=0.215$).

Table 5-1 Changes in haemodynamic and functional parameters after percutaneous mitral valve intervention.

Parameter	Baseline	6-months	P value
Systolic BP (mm/Hg)	126±15	135±13	0.333
Diastolic BP (mm/Hg)	72±10	78±8	0.268
Heart rate (bpm)	73±7	71±15	0.568
Haemoglobin (g/L)	120±24	137±24	0.062
Creatinine (umol/L)	113±37	122±46	0.215
6-minute walk test distance (m)	205±101	269±64	0.016
NHYA			
I	0	4	
II	3	5	0.019
III	6	1	
IV	1	0	

Abbreviations: BP, blood pressure; bpm, beats per minute; NYHA, New York Heart association functional class; m, metres.

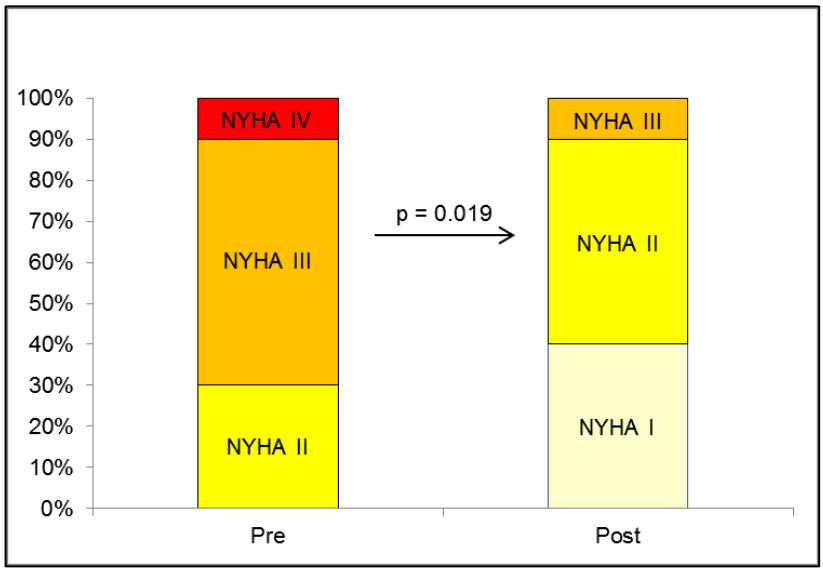


Figure 5-1 Changes in New York Heart Association (NYHA) functional class from pre to post percutaneous mitral valve intervention.

5.4.3 Follow up CMR data

Baseline and follow up post percutaneous mitral valve intervention CMR derived cardiac indices are presented in Table 5-2. Percutaneous mitral valve intervention resulted in a significant decrease in LVEDVi (118±23ml/m^2 to 92±28ml/m^2, p=0.001) and LVESVi (59±20ml/m^2 to 47±21ml/m^2, p=0.005), but no change to LVEF (51±11% to 50±8%, p=0.661) (Figure 5-2). Indexed LV mass (LVMi) remained unchanged (73±19g/m^2 to 68±21g/m^2, p=0.181). Right ventricular parameters remained unchanged, except for a significant increase in RVEF (43±8.3% to 50±9%, p=0.035) (Figure 5-2). There were no significant changes in indexed LA volumes (105±41ml/m^2 to 101±32ml/m^2, p=0.677) or indexed right atrial area (17±4.2cm^2/m^2 to 17±3.3cm^2/m^2, p=0.777) (Figure 5-3). Quantitated MR decreased with a decrease in MR-Rvol (55±23ml to 23±13ml, p=0.005) and MR-RF (51±9% to 29±15%, p<0.001) (Figure 5-4); there were no significant changes in quantified aortic, pulmonary or tricuspid regurgitation (Table 5-2).

Table 5-2 Comparison of baseline and follow up cardiac parameters assessed by CMR imaging

	Baseline	Follow up	p-value
LVEDVi (ml/m^2)	118±23	92±28	0.001
LVESVi (ml/m^2)	59±20	47±21	0.005
LVSVi (ml/m^2)	59±14	45±11	0.005
LVEF (%)	51±11	50±8	0.661
LVMi (g/m^2)	73±19	68±21	0.181
LAV-i (ml/m^2)	105±41	101±32	0.677
AR Rvol (ml)	5.1±4.1	4.9±3.4	0.878
AR RF (%)	10±8.9	9.6±7.2	0.959
MR Rvol (ml)	55±23	23±13	0.005
MR RF (%)	51±9	29±15	<0.001
RVEDVi (ml/m^2)	100±29	100±29	0.575
RVESVi (ml/m^2)	59±27	53±22	0.169
RVSVi (ml/m^2)	41±6.9	47±8	0.144
RVEF (%)	43±8.3	50±9	0.035
Pulm Rvol (ml)	3.1±3.0	2.1±2.1	0.139
Pulm RF (%)	6.3±5.3	4.4±4.8	0.241
TR Rvol (ml)	20±16	23±11	0.554
TR RF (%)	25±21	29±19	0.241
RAAi (cm^2/m^2)	17±4.2	17±3.3	0.777

Abbreviations: AR, aortic regurgitation; EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; i, indexed to body surface area; LAV, left atrial volume; LV, left ventricular; LVM, left ventricular mass; MR, mitral regurgitation; PR, pulmonary regurgitation; RAA, right atrial area; RF, regurgitant fraction; Rvol, regurgitant volume; RV, right ventricular; SV, stroke volume; TR, tricuspid regurgitation.

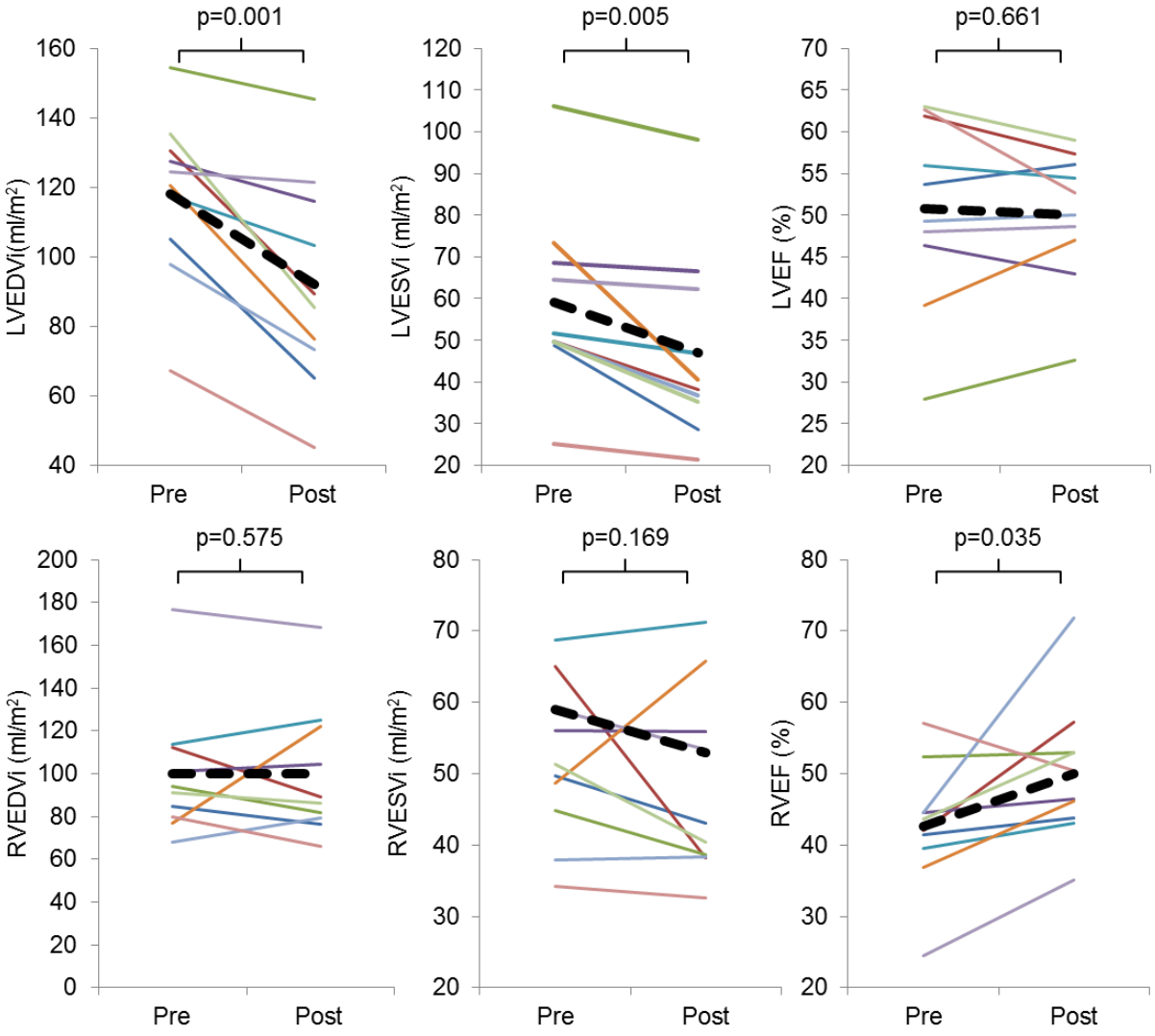


Figure 5-2 Line graphs depicting biventricular remodelling post percutaneous mitral intervention

Mean values depicted by dashed black line. Abbreviations: EDV, end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; i, indexed to body surface area; LV, left ventricular; RV, right ventricular.

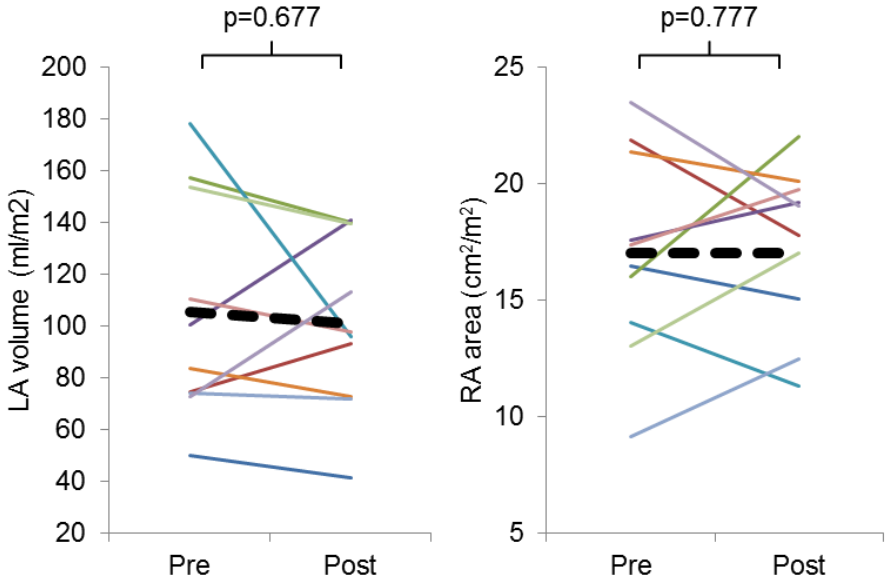


Figure 5-3 Line graphs depicting changes in indexed bi-atrial dimensions post percutaneous mitral intervention.

Mean values depicted by dashed black line. Abbreviations: LA, left atrium; RA, right atrium.

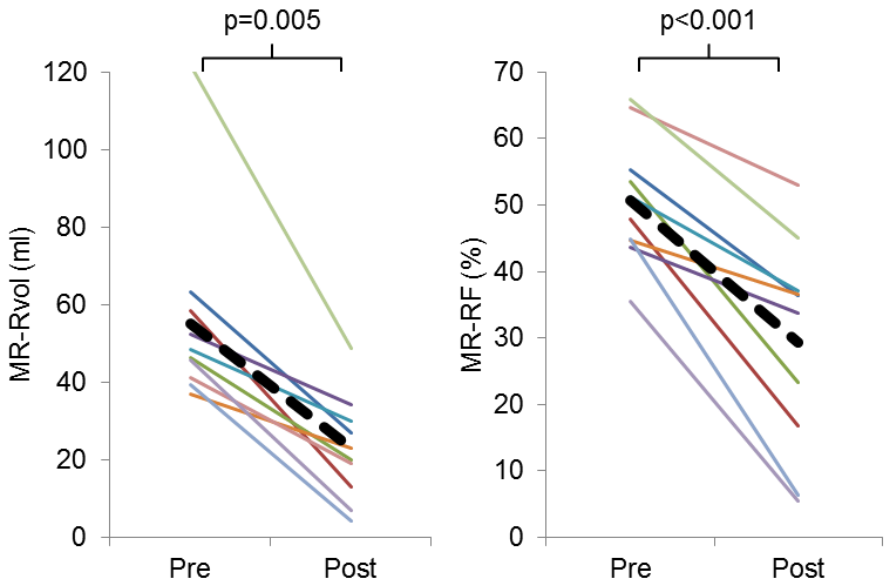


Figure 5-4 Line graphs depicting changes in quantitated MR post percutaneous mitral valve intervention.

Mean values depicted by dashed black line. Abbreviations: MR-Rvol, Mitral regurgitant volume, MR-RF, mitral regurgitant fraction.

5.5 Discussion

To our knowledge, despite the small sample size, this is the largest CMR study to assess changes to biventricular volumes, bi-atrial size and quantitate valvular flow using baseline and follow up CMR in a focussed cohort of primary MR patients. Importantly, recruitment to the study is ongoing to increase the sample size. Our findings are supportive of the use of percutaneous mitral valve intervention in the treatment of high risk primary MR patients both in terms of functional improvements and cardiac reverse remodelling.

5.5.1 Functional outcomes

NYHA functional class and 6MWT distances improved after percutaneous mitral valve intervention. This is in keeping with previous studies with well documented improvements in NYHA functional class (143, 357, 364, 366) and 6MWT distances (366, 367) post percutaneous mitral valve intervention for MR.

5.5.2 Cardiac reverse remodelling

5.5.2.1 Left ventricular remodelling

Our study demonstrated positive left-ventricular reverse remodelling in primary MR patients treated with percutaneous mitral valve intervention. The findings of a reduction in LV dimensions are in keeping with previous studies that utilised percutaneous intervention to treat significant MR (362-364). With the MR reduction demonstrated in our patients, a consequent reduction in LV dimensions is expected, but is not always guaranteed and is dependent on baseline LV dimensions and function. Chronic volume overload occurs in chronic MR due to dissolution of collagen tissue resulting in reorganization and slippage of myocardial fibres which causes remodelling of the extracellular matrix (363). This compensatory response normalises wall stress resulting in an asymptomatic stage of MR. However, continued prolonged chronic volume overload can cause progressive LV dilatation, stretching myocytes beyond their normal contractile length and can cause interstitial fibrosis and reduced myofibre content. The

decompensation of the dilating LV due to overload from chronic MR can then result in patients developing dyspnoea and exercise intolerance. Should intervention not be performed in timely manner when symptoms develop or LV dysfunction occurs, irreversible LV dysfunction can occur (11). This may be a result of chronic volume overload induced myocardial fibrosis, suggested by Velu *et al* who demonstrated worse LV remodelling and outcomes in MR patients with myocardial fibrosis identified by CMR compared with those without (368). Our study supports timely intervention, as our cohort only had mild LV dysfunction (LVEF 51% in context of significant MR), but all demonstrated reverse LV remodelling, evidenced by a reduction in LVEDVi and LVESVi in all patients as shown in Figure 5-2 and importantly no significant worsening of LVEF.

5.5.2.2 Right ventricular remodelling

We found no change in RV dimensions (RVEDVi/RVESVi) post percutaneous treatment for primary MR; this is in keeping with prior echocardiographic (369) and CMR studies (363, 364). Despite this, a significant increase in RVEF occurred, which was due to a non-significant fall in RVESVi. Similar findings of no change in RV dimensions but improved RV systolic function post MitraClip^{TM} have been demonstrated in a previous echocardiographic study. Gianni *et al* performed TTE at baseline and 6-months post MitraClip^{TM} in 35 patients with significant functional MR. They found TAPSE increased from 16.8±3.9mm to 19.3±4.5mm and PASP decreased from 50.1±6.8mmHg to 38.1±6.8mmHg from baseline to 6-months respectively post MitraClip^{TM}, but RV dimensions remained unchanged (370). The results suggest that reductions in MR after MitraClip^{TM} may not be sufficient to reduce RV end-diastolic volumes, but sufficient enough to allow an improvement in RVEF, which may be mediated by reduced PASP. Additionally, the findings of no significant alteration in RV volumes are in keeping with surgical patients (MVr/MVR) presented in Chapter 4.

5.5.2.3 Bi-atrial remodelling

This is the first CMR study to assess changes in right atrial size post percutaneous intervention. We demonstrated no significant change in bi-atrial size, in terms of indexed left atrial volumes and right atrial area, after percutaneous intervention. Prior studies demonstrate conflicting LA remodelling results post percutaneous intervention. Krumm *et al* and Brouwer *et al* both demonstrated a significant decrease in LA size, but used comparatively suboptimal methodology to ours, the former using CMR to assess LA area and the latter TTE to assess indexed left atrial volumes (360, 362). Given CMR is the reference standard for cardiac volume assessment (51), TTE biplane assessment underestimates atrial volumes and has worse intra/inter-observer variability compared with CMR biplane measurements (371) and LA volumes are a more robust marker of cardiovascular outcomes than LA area (372), then our use of CMR to perform area-length bi-plane atrial volume measurements is arguably the more robust methodology. Indeed our findings mirror that of Radunski *et al* (363), who similarly utilised CMR to perform bi-plane LA volume measurements. The advanced age and comorbidities of our study cohort may have impacted on the lack of LA reverse remodelling. Song *et al* demonstrated that increasing age, increasing pre-operative LA volume and the presence of AF and hypertension adversely affect LA reverse remodelling (373). Therefore our populations age (82±5 years), severe pre-intervention LA dilatation (105±41ml/m^2) and presence of AF in 80% and history of hypertension in 50% of patients, may have negatively impacted LA reverse remodelling.

5.5.2.4 Changes in valvular flow

Quantitated MR (MR-Rvol/MR-RF) reduced in all patients (Figure 5-4). However, percutaneous mitral intervention had no effect on quantitated aortic, pulmonary or tricuspid regurgitant volumes/fraction. Significant changes in AR or PR after surgery/intervention for mitral regurgitation are not expected or previously reported. Conversely TR can improve post mitral valve repair, as described in an echocardiographic study by Desai *at a*l (374). TR associated with MR can be multifactorial but is most often functional, where MR results in increased LA

pressure, causing increased pulmonary artery pressures, resultant RV dilatation/dysfunction and tricuspid annular dilatation causing functional TR. MR also causes LA dilatation, increasing the likelihood of AF, which in turn can cause RA dilatation, therefore tricuspid annular dilatation and resultant functional TR (375). Correction of MR can therefore theoretically reduce TR. However no such changes have been demonstrated post MitraClip in both echocardiographic (369, 376) and CMR studies (364). Toyoyama *et al* investigated 102 MR patients (Primary MR 37%, secondary MR 63%) by TTE at baseline and 1-year post MitraClip^{TM}; TR regressed in 26%, remained unchanged in 62% and worsened in 16% of patients. The lack of a reduction in TR may also be due to incomplete resolution of MR and therefore less significant reductions in RV afterload/PASP that can occur post mitral valve surgery. However, it may also be a result of non-significant baseline TR in the group, with mean quantitated TR-RF of 25%.

5.5.3 Limitations

The main limitation of this study is the small sample size. However, in the context of prior CMR studies assessing primary MR patients post percutaneous intervention the sample size is comparatively large. Lurz *et al* and Radunski *et al* only included 5 primary MR patients (363, 364). Only Krumm *et al* had a larger cohort of primary MR patients (n=13), but did not assess RV remodelling or quantitate MR changes (362). Therefore, to date, our study has the largest cohort of primary MR patients treated percutaneously in whom biventricular remodelling and changes in quantitated MR have been simultaneously assessed by CMR. Additionally, this is the first CMR study to focus solely on changes in primary MR patients post percutaneous mitral intervention, rather than perform pooled analysis and assess changes in right atrial size using CMR. However, clearly a larger cohort of patients would improve the generalisability of the results and may highlight statistically significant changes in cardiac parameters not visible at this cohort size. Indeed, left atrial volumes decreased, but were not statistically significant, which may be altered by a larger sample size. Recruitment in the study is ongoing to address this issue.

One patient dropped out after suffering partial MitraClip™ detachment and declined follow up imaging, excluding them from analysis. Such occurrences could result in survivor bias, as negative clinical outcomes resulted in exclusion and this patient may have demonstrated different remodelling to those with positive clinical outcomes. Therefore the results must be carefully interpreted as demonstrating a positive cardiac reverse remodelling in patients successfully treated with percutaneous mitral valve interventions.

5.5.4 Clinical implications

The study demonstrated positive LV reverse remodelling and MR reduction in all patients, which is a positive result for expanding the routine use of percutaneous interventions in primary MR patients not suitable for surgical intervention. Further research is required with additional patients to further study this cohort of patients, to allow in depth analysis of pre-procedural predictors of outcomes to further guide optimal patient selection. The study investigated patients that had either MitraClip™ or TMVI. With only one TMVI patient, comparisons between the two techniques could not be done. Future studies comparing varying percutaneous techniques to treat primary MR are required to further assess the differences and highlight which patients benefit greater from which technique.

5.6 Conclusion

Primary MR patients treated with percutaneous mitral valve intervention with good technical success benefit from left ventricular reverse remodelling, reduced MR, improved RV function and functional status. Larger studies using the reference standard (CMR) are now required to investigate if our positive results are repeated, allow more in-depth analysis and compare varying percutaneous techniques to guide optimal patient selection.

Chapter 6 Overall Discussion

Primary mitral regurgitation is a progressive disease, which left untreated can progress to significant morbidity and death (11). Surgical intervention is an effective treatment option. However, accurate imaging is pivotal to guide optimal management including patient selection and timing of surgical intervention or percutaneous intervention, if a patient's surgical risk deemed too high (1, 37). TTE is a widely available first line investigation for MR assessment and exercise-TTE can provide additional prognostic information to assist decision making (85-90). However, TTE can be limited by poor acoustic windows and Doppler alignment issues to quantitate MR using geometric assumptions which reduce accuracy and reproducibility (38, 50). CMR is the reference standard for biventricular assessment (51, 52) and demonstrates superior reproducibility (59, 60, 62, 63) and prognostic ability of MR quantification compared with TTE (63, 64). Ex-CMR has been developing over the past 3 decades with recent advancements making clinical use more promising (93, 198). As such, CMR is a powerful tool for both clinical and research assessment of primary MR. The overarching aim of this thesis was to utilise existing CMR techniques and develop/validate new Ex-CMR techniques in the assessment of primary MR to improve the decision making tools available and assess the optimal treatment options available.

6.1 Exercise CMR

In Chapter 2 a novel free-breathing Ex-CMR protocol assessing biventricular function and great vessel flow was developed and validated in healthy volunteers, specifically using vendor provided sequences, a commercially available ergometer and standard analysis software to increase widespread attainability. The developed protocol was subsequently used in asymptomatic primary MR patients in Chapter 3 and demonstrated the feasibility of the technique in this cohort and revealed decreasing MR severity as a mechanism to augment effective forward LVEF in asymptomatic patients. The healthy volunteers in Chapter 2 underwent a similar supine Ex-CMR protocol to the primary MR patients in Chapter 3. Therefore

comparisons can be made. However, there are some important caveats that prevent a direct comparison with statistical assessment and why the 2 cohorts are not presented in the same study: 1, the healthy volunteers are significantly younger and physically fitter, performing more regular exercise and 2, the healthy volunteers underwent a longer duration of exercise, as it was a protocol development study utilising more sequences and additionally assessing pulmonary flow. Both MR patients and healthy volunteers showed no change in LVEDVi with exercise. In contrast to healthy volunteers, the primary MR patients demonstrated no decrease in LVESVi, and no augmentation of LVSV or LVEF. The MR patients demonstrated no change in RVEDVi, whilst in healthy volunteers RVEDVi decreased. The differential findings in LV exercise haemodynamics are explainable by the variable LVCR found between primary MR patients (85, 86, 91). The explanation of an unchanged RVEDVi in MR patients compared with a decrease in healthy volunteers is less clear, but was similarly demonstrated by Chew *et al* (93) and potentially explainable by higher pulmonary pressures in MR patients. Pulmonary hypertension is a frequent consequence of significant MR which causes increased afterload on the RV (377) and can increase further during exercise (89, 90). This could theoretically prevent RVEDV decreasing during moderate supine exercise. Indeed in prior supine Ex-CMR studies, patients with significant pulmonary hypertension demonstrate an increase in RVEDVi and decrease in RVEF during exercise, compared with a decrease in RVEDVi and increase in RVEF in healthy volunteers (244, 268). Thus patients with mild pulmonary hypertension may theoretically exhibit an intermediate exercise response, as demonstrated in our primary MR patients, where RVEF augments, but not as significantly as healthy volunteers and RVEDVi remains unchanged. The ability to assess biventricular function and quantitate MR and effective forward LVEF during continuous supine Ex-CMR in primary MR patients brings Ex-CMR a step closer to the clinical domain. Further research using the developed protocol is required to assess the techniques prognostic ability and whether performing CMR at low intensity exercise provides added value or whether it can be removed to reduce total cycling time.

6.2 Mitral valve surgery/percutaneous intervention

Mitral valve repair, when feasible, is advised over mitral valve replacement in the treatment of primary MR (1, 39). Unfortunately no randomised trial has been performed to reinforce this guidance. Recent studies suggest prior comparative studies in favour of MVr may be a result of intrinsic bias (123, 125). As MVR patients are often older with more comorbidities (123) and many studies predated the routine use of chordal preservation techniques (116-119), which improves cardiac reverse remodelling post MVR (112-115, 342). As such, in Chapter 4 a comparison of cardiac reverse remodelling post MVr/MVR with chordal preservation was performed using a watchful waiting control group for comprehensive comparison. The study demonstrated equivalent left ventricular reverse remodelling between the surgical groups, with a greater augmentation of RVEF post MVR vs controls and lower residual quantitated MR post MVR. The results reinforce the need for large multicentre studies and potentially a randomised trial, to further assess MVr vs MVR with chordal preservation. The use of CMR in which is pivotal to ensure accurate assessment of cardiac reverse remodelling and quantitate MR.

Percutaneous interventions, such as the MitraClip^{TM}, are a novel treatment for the numerous patients deemed too high risk for surgical treatment of primary MR. Accurately assessing outcomes post percutaneous intervention is important to guide optimal patient selection and CMR offers superior reproducibility in MR quantification pre (59, 60, 62, 63) and post-percutaneous intervention to TTE (361). As such, CMR studies have investigated cardiac reverse remodelling post percutaneous intervention (362-364). However, none have published analysis in primary MR alone and as outcomes post percutaneous intervention can be significantly affected by underlying aetiology (162, 357, 360, 365), in Chapter 5 a focussed study assessing remodelling in primary MR was presented. Impressively, the study demonstrated left ventricular reverse remodelling and MR reduction in all patients. Further research is now required, to recruit a larger cohort, to allow in depth analysis of pre-procedural predictors of outcomes and compare the various percutaneous techniques available to further guide optimal patient selection.

As the primary MR patients that underwent percutaneous intervention in Chapter 5 had the identical CMR protocol performed to the control/MVr/MVR groups in Chapter 4, comparisons can be made. The caveats being the percutaneous group are significantly older, with more comorbidities that resulted in being declined surgical intervention, which may affect their cardiac reverse remodelling response and different statistical analysis was used in Chapter 4 & 5, therefore only cursory comparisons can be made. All intervention groups (MVr/MVR/percutaneous) demonstrated positive LV reverse remodelling with reductions in LVEDVi, whilst both surgical groups demonstrated reduced LVEF, the LVEF remained unchanged in the percutaneous group. This may be a result of less significant decreases in MR, with greater residual MR in the percutaneous group resulting in more offloading of LVSV into the left atrium. Indeed, left atrial reverse remodelling occurred in both surgical groups and not in the percutaneous group and may be, as described in Chapter 5.5.2.3, a result of greater residual MR, increased age and high incidence of AF blunting LA reverse remodelling in the percutaneous group. No intervention group (MVr/MVR/percutaneous) demonstrated statistically significant alterations in RV volumes. However, both surgical groups demonstrated a non-significant decreasing trend in RVEDVi, whilst mean RVEDVi of the percutaneous group remained exactly the same. Interestingly RVEF augmented in the MVR and percutaneous groups, but not the MVr group, despite lower residual MR in the MVr group. This may be a result of non-statistically significant increases in TR in the percutaneous group resulting in greater augmentation of RVEF, with more offloading into the RA, whilst both surgical groups demonstrated non-statistically significant decreases in TR. Indeed, both surgical groups had a mean residual TR-RF of 13% whilst the percutaneous group had a mean residual TR-RF of 29%. The results of greater MR reduction after surgical vs percutaneous intervention are in keeping with the EVEREST II trial and reinforce that percutaneous treatments should be reserved for those too high risk for surgical intervention, but that LV remodelling and MR reductions can still be achieved by this technique in this cohort (144).

6.3 General thesis discussion

The body of work presented in this thesis demonstrates a new method (Ex-CMR) via which primary MR patients can be investigated and challenges the current recommendation of MVr when feasible being universally superior to MVR. In addition to aspects discussed in Chapters 2 through 5 and sections 6.1 and 6.2, further insights are appreciated from this body of work when assessed as a whole and will be discussed below.

Timing of surgery for patients with primary MR is important, specifically deciding which patients benefit from early intervention. This thesis demonstrates how both resting and Ex-CMR could assist this decision and act as a powerful research tool for comparing treatment techniques.

As discussed in depth in section 1.1.3, CMR provides MR quantification with superior reproducibility and prognostic ability to TTE. Additionally, resting TTE utilises an integrated assessment of multiple measurements, as no single measurement is universally reliable in all patients/types of regurgitant jets. As such TTE assessment of MR is reliant on a subjective combination of each measurement, weighing up the caveats of each measurement in that individual, to determine severity. It is therefore not surprising that studies using CMR to assess outcomes could provide comparatively controversial results to TTE studies. The results highlighted in Chapter 4 pose a challenge to the current surgical recommendations, with MVR being deemed comparable to MVr as regards reverse remodelling but with greater residual MR post MVr. Indeed, these results are likely highlighted because of the greater accuracy of CMR to quantify MR than TTE. It is therefore arguable that future studies assessing MR patients should utilise CMR for the optimal assessment of MR severity and remodelling pre and post an intervention. Indeed, for research studies to accurately compare different percutaneous interventions for treatment of primary MR, the greater reproducibility/accuracy of MR quantification by CMR is likely essential due to the smaller decreases in MR often achieved, often smaller sample sizes and greater confounding variables due to being performed in an older population with more comorbidity. As regards routine clinical use of CMR, as previously discussed by

Uretsky et al (59, 72), it is reasonable to predict after further research, CMR be indicated to assess MR severity in cases where TTE/TOE assessment does not unequivocally define MR as severe before surgical intervention.

Theoretically an accurate exercise cardiac imaging modality should highlight predictors of asymptomatic MR patients more prone to deteriorate earlier than resting imaging and therefore assist patient selection for early surgical intervention. As presented, exercise echocardiography provides additional prognostic insight to resting TTE (1, 37, 85-90) but does not currently feature in international guideline decision to treat cascade pathways. This is partly a result of limitations regarding acoustic windows and reproducibility in clinical patients (92). As such a clinically viable Ex-CMR protocol is inviting. The first step towards a clinically viable Ex-CMR protocol for use in MR patients has been developed within this body of work. Further research is needed to build upon this work to move Ex-CMR into the clinical realm of primary MR assessment. The identification of effective forward LVEF as a highly reproducible measurement during Ex-CMR may help this become a reality. As discussed, effective forward LVEF takes into account changes in MR and LVEF, providing a single indices depicting ‘true’ forward flow with prognostic ability demonstrated in resting CMR (325). Ex-CMR studies assessing the prognostic utility of this measurement are now required. The ability to reliably measure changes in both LVEF and MR with a single index during exercise may prove beneficial, especially given the caveats highlighted above with TTE resting and exercise assessment.

In addition to recognising the importance of LV remodelling and changes in quantified MR, the results of this thesis highlight the importance of the right ventricle in patients with MR. As discussed in Chapter 6.1, one main difference between response to Ex-CMR between healthy volunteers in Chapter 2 and MR patients in Chapter 3 was changes in RVEDVi. Additionally, in Chapter 4 both surgical groups demonstrated significantly poorer baseline RVEF to the less symptomatic control group and post MVr patients demonstrated greater residual MR vs MVR patients and poorer follow-up RVEF (compared with controls). Yet comparable follow up RVEF was found between the MVR and control groups, additionally suggesting a causal link between MR severity and RVEF. Therefore

changes in RV size/function, as assessed by CMR, may be a precursor to symptom development/deterioration in primary MR patients. This is not a novel appreciation, with prior exercise TTE studies (87) demonstrating the prognostic importance of the right ventricle. Indeed, deterioration in RV size and function is partly mediated by pulmonary hypertension (377) and current guidelines advise considering early intervention in asymptomatic patients with PASP>50mmHg (1, 39). Given CMR offers reference standard assessment of the right ventricle and TTE assessment of PASP is reliant on an accurate Doppler tracing not achievable in every patient, then CMR assessment of RV function could form an important role in future prognostic assessment of MR patients, alongside the assessment of LV size/function and MR quantification. Further research using CMR to accurately assess the prognostic insight that changes in right ventricular size/function provides over time and during Ex-CMR are now required.

Chapter 7 Thesis conclusion

Mitral regurgitation is a heterogeneous disease with multiple aetiologies and variables that effect prognosis and outcomes post-surgery/intervention. Accuracy of investigations guiding management decisions and assessing research outcomes is therefore essential. CMR is the reference standard for biventricular assessment and offers superior reproducibility of MR quantification to TTE and therefore ideal to supplement echocardiography to optimise decision making and assess cardiac reverse remodelling research outcomes. In borderline cases, performing exercise cardiac imaging can provide additional prognostic information. Ex-CMR has developed over the past 3 decades as an option to combine the superior image quality of CMR with the preferred method of stress. However, imaging during continuous Ex-CMR comes with numerous challenges. With increasing exercise intensity, physical motion, respiratory motion and ECG gating artefacts increase, making image acquisition and analysis more difficult. The use of un-gated real-time techniques overcomes this issue, but requires prolonged analysis time, specialist sequences and software, reducing routine clinical utility. Within this body of work, an Ex-CMR technique utilizing vendor provided C-SENSE pulse sequences with retrospective cardiac gating and respiratory navigation, commercially available equipment and software to assess biventricular volumes and great vessel flow was developed and validated in healthy volunteers. Feasibility of the developed Ex-CMR protocol was subsequently proven in primary MR patients, demonstrating good/excellent reproducibility and that decreasing MR in this cohort allowed augmentation of effective forward LVEF. The technique now warrants further research to assess its prognostic ability in primary MR patients and feasibility in other valve diseases and congenital heart disease.

In primary MR patients, on sequential CMR, no significant difference in LV reverse remodelling was found post MVr vs MVR with chordal preservation. However, MVR resulted in superior RVEF (compared with controls) and less residual MR. Therefore, MVR may offer comparable cardiac reverse remodelling to MVr. Given MVr is advised first line whenever feasible, larger, multicentre research is now warranted, to assess whether the guidance can be downgraded to allow direct

replacements of more complex pathologies, reducing surgical times, without necessarily adversely impacting reverse remodelling. When primary MR patients are deemed too high risk for surgery, percutaneous mitral valve intervention is a useful treatment option, where achieving good technical success offers a reduction in MR, left ventricular reverse remodelling, improved RV function and functional status.

7.1 Future directions

In addition to the future applications of the work presented throughout this thesis, further studies and developments are required to progress CMR and Ex-CMR as a clinical and research tool in the assessment of primary MR patients. These potential future developments will be discussed below and possible future studies indicated directly from the body of work in this thesis shall be discussed in section 7.1.1.

CMR has developed as a useful adjunct to assess MR severity in borderline cases or where there is uncertainty of MR severity after TTE assessment. Although MR quantification by CMR has demonstrated superior prognostic ability to TTE (63, 64), limited studies determining how to accurately grade MR severity by CMR have been performed. Therefore, further studies to define MR severity by CMR MR quantification are required to improve the clinical utility of CMR across the entire MR severity spectrum. Once such studies have been completed and MR severity definitions by CMR are clearer a randomised TTE vs CMR guided surgery/intervention study may prove beneficial. Given the results highlighted in two studies by Urestky *et al*, demonstrated only 32-37% of patients undergoing mitral valve surgery for TTE defined significant MR had severe MR by CMR assessment (59, 72) and prior prospective observational studies demonstrated superior prognostic ability via CMR vs TTE (63, 64), then CMR MR severity assessment may better guide the need for surgical intervention.

4D Flow CMR refers to PCMR with flow-encoding in all three spatial directions, resolved relative to all three dimensions of space and to the dimension of time along the cardiac cycle (378). It allows dynamic visualization of flow in multiple

orientations and accurate and reproducible quantification of MR using the retrospective valve tracking method. The technique potentially allows more accurate direct quantification of MR compared with 2D PCMR sequences, especially in MR jets that change direction and shape significantly during systole, which occur more commonly in primary MR (379). Further research is required to assess whether 4D-flow MR quantification provides additional/superior prognostic information to standard 2D PCMR techniques, but the technique demonstrates significant promise. The recent demonstration of feasibility of 4D flow assessment during supine Ex-CMR is exciting (300). Technological developments to hasten acquisition times and further research assessing feasibility in patients with MR are required to assess the potential clinical utility of the technique.

7.1.1 Potential future studies

Based on the body of work presented in this thesis, several future studies could progress the field of CMR and Ex-CMR in the optimal management of primary MR patients.

Future Ex-CMR studies are required to build upon the feasibility studies presented in Chapters 2&3. The feasibility of accurate and reproducible assessment of other valve diseases and structural heart disease with the validated CS3 Ex-CMR protocol is indicated. Insights from Chapters 2&3 suggest the protocol should be widely applicable and useful in a wide range of valve diseases and structural heart disease. Larger studies to assess the prognostic utility of Ex-CMR in primary MR patients are indicated. The additional prognostic information exercise-TTE affords over resting TTE suggests Ex-CMR may become a useful prognostic tool in the future. Ex-CMR could potentially identify primary MR patients who benefit from early surgical intervention, thus justifying intervention before cardiac decompensation, reducing peri-operative risks and improving long term clinical outcomes. As such, future studies are indicated performed in the following order if positive results in the initial studies:

1. Larger Ex-CMR studies assessing prognostic ability of the CS3 Ex-CMR protocol in primary MR patients, with the performance of baseline Ex-CMR

and observation for outcomes including development of symptoms or need for mitral valve surgery.

2. Exercise-TTE vs Ex-CMR observational studies to compare prognostic ability and define any prognostic cut offs for clinical use in primary MR patients.

The results presented in Chapter 4 demonstrating equivalent cardiac reverse remodelling between MVr and MVR with chordal preservation, but greater residual MR post MVr require further studies. If the results are replicated in larger multicentre studies, the current guidelines of repair whenever feasible could be relaxed, initially to allow direct MVR in elderly patients in whom a tissue MVR would last a lifetime or patients with a current indication for anticoagulation. This may allow for reduced surgical times, peri-operative risk and at least equivalent cardiac reverse remodelling and thus potentially clinical outcomes. As such, future studies are indicated to further question superiority between MVr and MVR with chordal preservation, performed in the following order if positive results in the initial studies:

1. Multicentre studies comparing MVr vs MVR with chordal preservation in primary MR patients, using CMR to assess remodelling and prolonged follow up to assess clinical outcomes.
2. Randomised control trials comparing MVr vs MVR with chordal preservation with recruitment criteria defined by prior multi-centre studies.

Finally, the use and variety of percutaneous interventions to treat primary MR is increasing. As demonstrated in the differing results between MITRA-FR and COAPT trials, careful patient selection is vital to ensure optimal outcomes (145-147). As shown in Chapter 5, percutaneous mitral valve intervention can result in a reduction in MR and positive cardiac reverse remodelling. Further research assessing predictors of favourable outcomes and compare the varying and emerging percutaneous interventions are required to help guide patient selection and optimal patient management. CMR is a vital tool in future studies due to the multiple benefits in MR and biventricular assessment presented throughout this thesis. As often smaller improvements are seen post percutaneous than surgical

intervention and are performed in older populations with greater co-morbidities and thus confounding variables. As such future comparative percutaneous studies require an imaging modality with excellent reproducibility/accuracy to highlight differences between treatments.

With further research, CMR and Ex-CMR has the potential to significantly improve patient selection for early intervention, guide optimal surgical management strategies and therefore improve long term outcomes and quality of life in patients with primary MR.

References

1. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J. 2017;38(36):2739-91.
2. Turi Zoltan G. Mitral Valve Disease. Circulation. 2004;109(6):e38-e41.
3. Stone GW, Vahanian AS, Adams DH, Abraham WT, Borer JS, Bax JJ, et al. Clinical Trial Design Principles and Endpoint Definitions for Transcatheter Mitral Valve Repair and Replacement: Part 1: Clinical Trial Design Principles: A Consensus Document From the Mitral Valve Academic Research Consortium. J Am Coll Cardiol. 2015;66(3):278-307.
4. McCarthy KP, Ring L, Rana BS. Anatomy of the mitral valve: understanding the mitral valve complex in mitral regurgitation. Eur J Echocardiogr. 2010;11(10):i3-9.
5. van Rijk-Zwikker GL, Delemarre BJ, Huysmans HA. Mitral valve anatomy and morphology: relevance to mitral valve replacement and valve reconstruction. J Card Surg. 1994;9(2 Suppl):255-61.
6. O'Gara P, Sugeng L, Lang R, Sarano M, Hung J, Raman S, et al. The role of imaging in chronic degenerative mitral regurgitation. JACC Cardiovasc Imaging. 2008;1(2):221-37.
7. Carpentier AF, Lessana A, Relland JY, Belli E, Mihaileanu S, Berrebi AJ, et al. The "physio-ring": an advanced concept in mitral valve annuloplasty. Ann Thorac Surg. 1995;60(5):1177-85; discussion 85-6.
8. Voci P, Bilotta F, Caretta Q, Mercanti C, Marino B. Papillary Muscle Perfusion Pattern. Circulation. 1995;91(6):1714-8.
9. Carpentier A. Cardiac valve surgery--the "French correction". J Thorac Cardiovasc Surg. 1983;86(3):323-37.
10. de Marchena E, Badiye A, Robalino G, Junttila J, Atapattu S, Nakamura M, et al. Respective Prevalence of the Different Carpentier Classes of Mitral Regurgitation: A Stepping Stone for Future Therapeutic Research and Development. J Card Surg. 2011;26(4):385-92.
11. Nishimura RA, Vahanian A, Eleid MF, Mack MJ. Mitral valve disease--current management and future challenges. Lancet. 2016;387(10025):1324-34.
12. Anyanwu AC, Adams DH. Etiologic classification of degenerative mitral valve disease: Barlow's disease and fibroelastic deficiency. Semin Thorac Cardiovasc Surg. 2007;19(2):90-6.
13. Barlow JB, Bosman CK. Aneurysmal protrusion of the posterior leaflet of the mitral valve. An auscultatory-electrocardiographic syndrome. Am Heart J. 1966;71(2):166-78.
14. Disse S, Abergel E, Berrebi A, Houot AM, Le Heuzey JY, Diebold B, et al. Mapping of a first locus for autosomal dominant myxomatous mitral-valve prolapse to chromosome 16p11.2-p12.1. Am J Hum Genet. 1999;65(5):1242-51.
15. Harb SC, Griffin BP. Mitral Valve Disease: a Comprehensive Review. Curr Cardiol Rep. 2017;19(8):73.
16. Shah PM. Current concepts in mitral valve prolapse--diagnosis and management. J Cardiol. 2010;56(2):125-33.
17. Fornes P, Heudes D, Fuzellier JF, Tixier D, Bruneval P, Carpentier A. Correlation between clinical and histologic patterns of degenerative mitral valve insufficiency: a histomorphometric study of 130 excised segments. Cardiovasc Pathol. 1999;8(2):81-92.
18. Seckeler MD, Hoke TR. The worldwide epidemiology of acute rheumatic fever and rheumatic heart disease. Clin Epidemiol. 2011;3:67-84.
19. Marcus RH, Sareli P, Pocock WA, Meyer TE, Magalhaes MP, Grieve T, et al. Functional anatomy of severe mitral regurgitation in active rheumatic carditis. Am J Cardiol. 1989;63(9):577-84.

20. Marcus RH, Sareli P, Pocock WA, Barlow JB. The spectrum of severe rheumatic mitral valve disease in a developing country. Correlations among clinical presentation, surgical pathologic findings, and hemodynamic sequelae. Ann Intern Med. 1994;120(3):177-83.
21. Zuhlke L, Engel ME, Karthikeyan G, Rangarajan S, Mackie P, Cupido B, et al. Characteristics, complications, and gaps in evidence-based interventions in rheumatic heart disease: the Global Rheumatic Heart Disease Registry (the REMEDY study). Eur Heart J. 2015;36(18):1115-22a.
22. Remenyi B, ElGuindy A, Smith SC, Jr., Yacoub M, Holmes DR, Jr. Valvular aspects of rheumatic heart disease. Lancet. 2016;387(10025):1335-46.
23. Essop MR, Peters F. Contemporary issues in rheumatic fever and chronic rheumatic heart disease. Circulation. 2014;130(24):2181-8.
24. Nappi F, Spadaccio C, Dreyfus J, Attias D, Acar C, Bando K. Mitral endocarditis: A new management framework. J Thorac Cardiovasc Surg. 2018;156(4):1486-95 e4.
25. Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta JP, Del Zotti F, et al. 2015 ESC Guidelines for the management of infective endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). Eur Heart J. 2015;36(44):3075-128.
26. DePasquale NP, Burch GE. Papillary muscle dysfunction in coronary (ischemic) heart disease. Annu Rev Med. 1971;22:327-42.
27. Nishimura RA, Gersh BJ, Schaff HV. The case for an aggressive surgical approach to papillary muscle rupture following myocardial infarction: "From paradise lost to paradise regained". Heart. 2000;83(6):611-3.
28. Ciarka A, Van de Veire N. Secondary mitral regurgitation: pathophysiology, diagnosis, and treatment. Heart. 2011;97(12):1012-23.
29. Bursi F, Enriquez-Sarano M, Nkomo VT, Jacobsen SJ, Weston SA, Meverden RA, et al. Heart failure and death after myocardial infarction in the community: the emerging role of mitral regurgitation. Circulation. 2005;111(3):295-301.
30. Levine RA, Schwammenthal E. Ischemic mitral regurgitation on the threshold of a solution: from paradoxes to unifying concepts. Circulation. 2005;112(5):745-58.
31. Deferm S, Bertrand PB, Verbrugge FH, Verhaert D, Rega F, Thomas JD, et al. Atrial Functional Mitral Regurgitation: JACC Review Topic of the Week. J Am Coll Cardiol. 2019;73(19):2465-76.
32. Watanabe N, Maltais S, Nishino S, O'Donoghue TA, Hung J. Functional Mitral Regurgitation: Imaging Insights, Clinical Outcomes and Surgical Principles. Prog Cardiovasc Dis. 2017;60(3):351-60.
33. Debonnaire P, Al Amri I, Leong DP, Joyce E, Katsanos S, Kamperidis V, et al. Leaflet remodelling in functional mitral valve regurgitation: characteristics, determinants, and relation to regurgitation severity. Eur Heart J Cardiovasc Imaging. 2015;16(3):290-9.
34. Rossi A, Dini FL, Faggiano P, Agricola E, Cicoira M, Frattini S, et al. Independent prognostic value of functional mitral regurgitation in patients with heart failure. A quantitative analysis of 1256 patients with ischaemic and non-ischaemic dilated cardiomyopathy. Heart. 2011;97(20):1675-80.
35. Packer M, Grayburn PA. Contrasting Effects of Pharmacological, Procedural, and Surgical Interventions on Proportionate and Disproportionate Functional Mitral Regurgitation in Chronic Heart Failure. Circulation. 2019;140(9):779-89.
36. Van De Heyning Caroline M, Bertrand Philippe B, Debonnaire P, De Maeyer C, Vandervoort Pieter M, Coussement P, et al. Mechanism of Symptomatic Improvement After Percutaneous Therapy for Secondary Mitral Regurgitation. J Am Coll Cardiol. 2016;68(1):128-9.
37. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, 3rd, Guyton RA, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a

report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Thorac Cardiovasc Surg. 2014;148(1):e1-e132.
38. Chew PG, Bounford K, Plein S, Schlosshan D, Greenwood JP. Multimodality imaging for the quantitative assessment of mitral regurgitation. Quant Imaging Med Surg. 2018;8(3):342-59.
39. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, 3rd, Fleisher LA, et al. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2017;70(2):252-89.
40. Zoghbi WA, Adams D, Bonow RO, Enriquez-Sarano M, Foster E, Grayburn PA, et al. Recommendations for Noninvasive Evaluation of Native Valvular Regurgitation: A Report from the American Society of Echocardiography Developed in Collaboration with the Society for Cardiovascular Magnetic Resonance. J Am Soc Echocardiogr. 2017;30(4):303-71.
41. Chambers JB, Garbi M, Nieman K, Myerson S, Pierard LA, Habib G, et al. Appropriateness criteria for the use of cardiovascular imaging in heart valve disease in adults: a European Association of Cardiovascular Imaging report of literature review and current practice. Eur Heart J Cardiovasc Imaging. 2017;18(5):489-98.
42. Zoghbi WA, Enriquez-Sarano M, Foster E, Grayburn PA, Kraft CD, Levine RA, et al. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and doppler echocardiography. J Am Soc Echocardiogr. 2003;16(7):777-802.
43. Roberts BJ, Grayburn PA. Color flow imaging of the vena contracta in mitral regurgitation: technical considerations. J Am Soc Echocardiogr. 2003;16(9):1002-6.
44. Hall SA, Brickner ME, Willett DL, Irani WN, Afridi I, Grayburn PA. Assessment of Mitral Regurgitation Severity by Doppler Color Flow Mapping of the Vena Contracta. Circulation. 1997;95(3):636-42.
45. Hundley WG, Kizilbash AM, Afridi I, Franco F, Peshock RM, Grayburn PA. Administration of an intravenous perfluorocarbon contrast agent improves echocardiographic determination of left ventricular volumes and ejection fraction: comparison with cine magnetic resonance imaging. J Am Coll Cardiol. 1998;32(5):1426-32.
46. Gutiérrez-Chico JL, Zamorano JL, Pérez de Isla L, Orejas M, Almería C, Rodrigo JL, et al. Comparison of left ventricular volumes and ejection fractions measured by three-dimensional echocardiography versus by two-dimensional echocardiography and cardiac magnetic resonance in patients with various cardiomyopathies. Am J Cardiol. 2005;95(6):809-13.
47. Bargiggia GS, Tronconi L, Sahn DJ, Recusani F, Raisaro A, De Servi S, et al. A new method for quantitation of mitral regurgitation based on color flow Doppler imaging of flow convergence proximal to regurgitant orifice. Circulation. 1991;84(4):1481-9.
48. Gardner MA, Hossack KF, Smith IR. Long-Term Results Following Repair for Degenerative Mitral Regurgitation - Analysis of Factors Influencing Durability. Heart Lung Circ. 2019;28(12):1852-65.
49. Grewal KS, Malkowski MJ, Piracha AR, Astbury JC, Kramer CM, Dianzumba S, et al. Effect of general anesthesia on the severity of mitral regurgitation by transesophageal echocardiography. Am J Cardiol. 2000;85(2):199-203.
50. Uretsky S, Argulian E, Narula J, Wolff SD. Use of Cardiac Magnetic Resonance Imaging in Assessing Mitral Regurgitation: Current Evidence. J Am Coll Cardiol. 2018;71(5):547-63.
51. Grothues F, Smith GC, Moon JCC, Bellenger NG, Collins P, Klein HU, et al. Comparison of interstudy reproducibility of cardiovascular magnetic resonance with two-

dimensional echocardiography in normal subjects and in patients with heart failure or left ventricular hypertrophy. Am J Cardiol. 2002;90(1):29-34.
52. Bellenger NG, Burgess MI, Ray SG, Lahiri A, Coats AJ, Cleland JG, et al. Comparison of left ventricular ejection fraction and volumes in heart failure by echocardiography, radionuclide ventriculography and cardiovascular magnetic resonance; are they interchangeable? Eur Heart J. 2000;21(16):1387-96.
53. Gulsin GS, Singh A, McCann GP. Cardiovascular magnetic resonance in the evaluation of heart valve disease. BMC medical imaging. 2017;17(1):67.
54. Stork A, Franzen O, Ruschewski H, Detter C, Mullerleile K, Bansmann PM, et al. Assessment of functional anatomy of the mitral valve in patients with mitral regurgitation with cine magnetic resonance imaging: comparison with transesophageal echocardiography and surgical results. European radiology. 2007;17(12):3189-98.
55. Pflugfelder PW, Sechtem UP, White RD, Cassidy MM, Schiller NB, Higgins CB. Noninvasive evaluation of mitral regurgitation by analysis of left atrial signal loss in cine magnetic resonance. Am Heart J. 1989;117(5):1113-9.
56. Chan KM, Wage R, Symmonds K, Rahman-Haley S, Mohiaddin RH, Firmin DN, et al. Towards comprehensive assessment of mitral regurgitation using cardiovascular magnetic resonance. J Cardiovasc Magn Reson. 2008;10:61.
57. Buchner S, Debl K, Poschenrieder F, Feuerbach S, Riegger GA, Luchner A, et al. Cardiovascular magnetic resonance for direct assessment of anatomic regurgitant orifice in mitral regurgitation. Circ Cardiovasc Imaging. 2008;1(2):148-55.
58. Krieger EV, Lee J, Branch KR, Hamilton-Craig C. Quantitation of mitral regurgitation with cardiac magnetic resonance imaging: a systematic review. Heart. 2016;102(23):1864-70.
59. Uretsky S, Gillam L, Lang R, Chaudhry FA, Argulian E, Supariwala A, et al. Discordance between echocardiography and MRI in the assessment of mitral regurgitation severity: a prospective multicenter trial. J Am Coll Cardiol. 2015;65(11):1078-88.
60. Cawley PJ, Hamilton-Craig C, Owens DS, Krieger EV, Strugnell WE, Mitsumori L, et al. Prospective comparison of valve regurgitation quantitation by cardiac magnetic resonance imaging and transthoracic echocardiography. Circ Cardiovasc Imaging. 2013;6(1):48-57.
61. Le Goffic C, Toledano M, Ennezat PV, Binda C, Castel AL, Delelis F, et al. Quantitative Evaluation of Mitral Regurgitation Secondary to Mitral Valve Prolapse by Magnetic Resonance Imaging and Echocardiography. Am J Cardiol. 2015;116(9):1405-10.
62. Lopez-Mattei JC, Ibrahim H, Shaikh KA, Little SH, Shah DJ, Maragiannis D, et al. Comparative Assessment of Mitral Regurgitation Severity by Transthoracic Echocardiography and Cardiac Magnetic Resonance Using an Integrative and Quantitative Approach. Am J Cardiol. 2016;117(2):264-70.
63. Penicka M, Vecera J, Mirica DC, Kotrc M, Kockova R, Van Camp G. Prognostic Implications of Magnetic Resonance-Derived Quantification in Asymptomatic Patients With Organic Mitral Regurgitation: Comparison With Doppler Echocardiography-Derived Integrative Approach. Circulation. 2018;137(13):1349-60.
64. Myerson SG, d'Arcy J, Christiansen JP, Dobson LE, Mohiaddin R, Francis JM, et al. Determination of Clinical Outcome in Mitral Regurgitation With Cardiovascular Magnetic Resonance Quantification. Circulation. 2016;133(23):2287-96.
65. Shiran A, Sagie A. Tricuspid regurgitation in mitral valve disease incidence, prognostic implications, mechanism, and management. J Am Coll Cardiol. 2009;53(5):401-8.
66. Cohen SR, Sell JE, McIntosh CL, Clark RE. Tricuspid regurgitation in patients with acquired, chronic, pure mitral regurgitation. I. Prevalence, diagnosis, and comparison of preoperative clinical and hemodynamic features in patients with and without tricuspid regurgitation. J Thorac Cardiovasc Surg. 1987;94(4):481-7.

67. Kon MWS, Myerson SG, Moat NE, Pennell DJ. Quantification of regurgitant fraction in mitral regurgitation by cardiovascular magnetic resonance: comparison of techniques. J Heart Valve Dis. 2004;13(4):600-7.
68. Polte CL, Bech-Hanssen O, Johnsson ÅA, Gao SA, Lagerstrand KM. Mitral regurgitation quantification by cardiovascular magnetic resonance: a comparison of indirect quantification methods. Int J Cardiovasc Imaging. 2015;31(6):1223-31.
69. Kramer CM, Barkhausen J, Bucciarelli-Ducci C, Flamm SD, Kim RJ, Nagel E. Standardized cardiovascular magnetic resonance imaging (CMR) protocols: 2020 update. J Cardiovasc Magn Reson. 2020;22(1):17.
70. Gelfand EV, Hughes S, Hauser TH, Yeon SB, Goepfert L, Kissinger KV, et al. Severity of mitral and aortic regurgitation as assessed by cardiovascular magnetic resonance: optimizing correlation with Doppler echocardiography. J Cardiovasc Magn Reson. 2006;8(3):503-7.
71. Aplin M, Kyhl K, Bjerre J, Ihlemann N, Greenwood JP, Plein S, et al. Cardiac remodelling and function with primary mitral valve insufficiency studied by magnetic resonance imaging. Eur Heart J Cardiovasc Imaging. 2016;17(8):863-70.
72. Uretsky S, Shah DJ, Lasam G, Horgan S, Debs D, Wolff SD. Usefulness of Mitral Regurgitant Volume Quantified Using Magnetic Resonance Imaging to Predict Left Ventricular Remodeling After Mitral Valve "Correction". Am J Cardiol. 2020;125(11):1666-72.
73. Hassan AKM, Algowhary MI, Kishk AYT, Youssef AAA, Razik NA. Cardiac magnetic resonance assessment of mitral regurgitation severity appears better than echocardiographic imaging. Int J Cardiovasc Imaging. 2020;36(5):889-97.
74. Kilner PJ, Gatehouse PD, Firmin DN. Flow Measurement by Magnetic Resonance: A Unique Asset Worth Optimising. J Cardiovasc Magn Reson. 2007;9(4):723-8.
75. Garg P, Swift AJ, Zhong L, Carlhäll C-J, Ebbers T, Westenberg J, et al. Assessment of mitral valve regurgitation by cardiovascular magnetic resonance imaging. Nature Reviews Cardiology. 2020;17(5):298-312.
76. Choi J, Heo R, Hong G-R, Chang H-J, Sung Ji M, Shin Sang H, et al. Differential Effect of 3-Dimensional Color Doppler Echocardiography for the Quantification of Mitral Regurgitation According to the Severity and Characteristics. Circulation: Cardiovascular Imaging. 2014;7(3):535-44.
77. Sköldborg V, Madsen PL, Dalsgaard M, Abdulla J. Quantification of mitral valve regurgitation by 2D and 3D echocardiography compared with cardiac magnetic resonance a systematic review and meta-analysis. Int J Cardiovasc Imaging. 2020;36(2):279-89.
78. Picano E, Pibarot P, Lancellotti P, Monin Jean L, Bonow Robert O. The Emerging Role of Exercise Testing and Stress Echocardiography in Valvular Heart Disease. J Am Coll Cardiol. 2009;54(24):2251-60.
79. Lancellotti P, Dulgheru R, Go YY, Sugimoto T, Marchetta S, Oury C, et al. Stress echocardiography in patients with native valvular heart disease. 2018;104(10):807-13.
80. Lancellotti P, Pellikka PA, Budts W, Chaudhry FA, Donal E, Dulgheru R, et al. The Clinical Use of Stress Echocardiography in Non-Ischaemic Heart Disease: Recommendations from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. J Am Soc Echocardiogr. 2017;30(2):101-38.
81. Oosterhof T, Tulevski, II, Roest AA, Steendijk P, Vliegen HW, van der Wall EE, et al. Disparity between dobutamine stress and physical exercise magnetic resonance imaging in patients with an intra-atrial correction for transposition of the great arteries. J Cardiovasc Magn Reson. 2005;7(2):383-9.
82. Varga A, Garcia MA, Picano E, International Stress Echo Complication R. Safety of stress echocardiography (from the International Stress Echo Complication Registry). Am J Cardiol. 2006;98(4):541-3.
83. Pellikka PA, Nagueh SF, Elhendy AA, Kuehl CA, Sawada SG, American Society of E. American Society of Echocardiography recommendations for performance,

interpretation, and application of stress echocardiography. J Am Soc Echocardiogr. 2007;20(9):1021-41.
84. Wolk MJ, Bailey SR, Doherty JU, Douglas PS, Hendel RC, Kramer CM, et al. ACCF/AHA/ASE/ASNC/HFSA/HRS/SCAI/SCCT/SCMR/STS 2013 multimodality appropriate use criteria for the detection and risk assessment of stable ischemic heart disease: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2014;63(4):380-406.
85. Lee R, Haluska B, Leung DY, Case C, Mundy J, Marwick TH. Functional and prognostic implications of left ventricular contractile reserve in patients with asymptomatic severe mitral regurgitation. Heart. 2005;91(11):1407-12.
86. Magne J, Mahjoub H, Dulgheru R, Pibarot P, Pierard LA, Lancellotti P. Left ventricular contractile reserve in asymptomatic primary mitral regurgitation. Eur Heart J. 2014;35(24):1608-16.
87. Kusunose K, Popovic ZB, Motoki H, Marwick TH. Prognostic significance of exercise-induced right ventricular dysfunction in asymptomatic degenerative mitral regurgitation. Circ Cardiovasc Imaging. 2013;6(2):167-76.
88. Magne J, Lancellotti P, Pierard LA. Exercise-induced changes in degenerative mitral regurgitation. J Am Coll Cardiol. 2010;56(4):300-9.
89. Magne J, Donal E, Mahjoub H, Miltner B, Dulgheru R, Thebault C, et al. Impact of exercise pulmonary hypertension on postoperative outcome in primary mitral regurgitation. Heart. 2015;101(5):391-6.
90. Suzuki K, Izumo M, Yoneyama K, Mizukoshi K, Kamijima R, Kou S, et al. Influence of exercise-induced pulmonary hypertension on exercise capacity in asymptomatic degenerative mitral regurgitation. J Cardiol. 2015;66(3):246-52.
91. Leung DY, Griffin BP, Stewart WJ, Cosgrove DM, 3rd, Thomas JD, Marwick TH. Left ventricular function after valve repair for chronic mitral regurgitation: predictive value of preoperative assessment of contractile reserve by exercise echocardiography. J Am Coll Cardiol. 1996;28(5):1198-205.
92. Coisne A, Levy F, Malaquin D, Richardson M, Quere JP, Montaigne D, et al. Feasibility of Doppler hemodynamic evaluation of primary and secondary mitral regurgitation during exercise echocardiography. Int J Cardiovasc Imaging. 2015;31(2):291-9.
93. Chew PG, Swoboda PP, Ferguson C, Garg P, Cook AL, Ibeggazene S, et al. Feasibility and reproducibility of a cardiovascular magnetic resonance free-breathing, multi-shot, navigated image acquisition technique for ventricular volume quantification during continuous exercise. Quant Imaging Med Surg. 2020;10(9):1837-51.
94. Enriquez-Sarano M, Akins CW, Vahanian A. Mitral regurgitation. Lancet. 2009;373(9672):1382-94.
95. Carpentier A, Deloche A, Dauptain J, Soyer R, Blondeau P, Piwnica A, et al. A new reconstructive operation for correction of mitral and tricuspid insufficiency. J Thorac Cardiovasc Surg. 1971;61(1):1-13.
96. Coutinho GF, Antunes MJ. Mitral valve repair for degenerative mitral valve disease: surgical approach, patient selection and long-term outcomes. Heart. 2017;103(21):1663-9.
97. Castillo JG, Anyanwu AC, Fuster V, Adams DH. A near 100% repair rate for mitral valve prolapse is achievable in a reference center: implications for future guidelines. J Thorac Cardiovasc Surg. 2012;144(2):308-12.
98. Goldstone AB, Cohen JE, Howard JL, Edwards BB, Acker AL, Hiesinger W, et al. A "Repair-All" Strategy for Degenerative Mitral Valve Disease Safely Minimizes Unnecessary Replacement. Ann Thorac Surg. 2015;99(6):1983-90; discussion 90-1.

99. David TE, Ivanov J, Armstrong S, Christie D, Rakowski H. A comparison of outcomes of mitral valve repair for degenerative disease with posterior, anterior, and bileaflet prolapse. J Thorac Cardiovasc Surg. 2005;130(5):1242-9.
100. Seeburger J, Borger MA, Doll N, Walther T, Passage J, Falk V, et al. Comparison of outcomes of minimally invasive mitral valve surgery for posterior, anterior and bileaflet prolapse. Eur J Cardiothorac Surg. 2009;36(3):532-8.
101. Castillo JG, Anyanwu AC, El-Eshmawi A, Adams DH. All anterior and bileaflet mitral valve prolapses are repairable in the modern era of reconstructive surgery. Eur J Cardiothorac Surg. 2014;45(1):139-45; discussion 45.
102. Vassileva CM, Boley T, Markwell S, Hazelrigg S. Impact of hospital annual mitral procedural volume on mitral valve repair rates and mortality. J Heart Valve Dis. 2012;21(1):41-7.
103. Bolling SF, Li S, O'Brien SM, Brennan JM, Prager RL, Gammie JS. Predictors of mitral valve repair: clinical and surgeon factors. Ann Thorac Surg. 2010;90(6):1904-11; discussion 12.
104. Sundermann SH, Sromicki J, Rodriguez Cetina Biefer H, Seifert B, Holubec T, Falk V, et al. Mitral valve surgery: right lateral minithoracotomy or sternotomy? A systematic review and meta-analysis. J Thorac Cardiovasc Surg. 2014;148(5):1989-95 e4.
105. Modi P, Hassan A, Chitwood WR, Jr. Minimally invasive mitral valve surgery: a systematic review and meta-analysis. Eur J Cardiothorac Surg. 2008;34(5):943-52.
106. van der Merwe J, Casselman F. Mitral Valve Replacement-Current and Future Perspectives. Open J Cardiovasc Surg. 2017;9:1179065217719023.
107. Salamon J, Munoz-Mendoza J, Liebelt JJ, Taub CC. Mechanical valve obstruction: Review of diagnostic and treatment strategies. World J Cardiol. 2015;7(12):875-81.
108. Chikwe J, Chiang YP, Egorova NN, Itagaki S, Adams DH. Survival and outcomes following bioprosthetic vs mechanical mitral valve replacement in patients aged 50 to 69 years. JAMA. 2015;313(14):1435-42.
109. Kaneko T, Cohn LH, Aranki SF. Tissue valve is the preferred option for patients aged 60 and older. Circulation. 2013;128(12):1365-71.
110. Hammermeister K, Sethi GK, Henderson WG, Grover FL, Oprian C, Rahimtoola SH. Outcomes 15 years after valve replacement with a mechanical versus a bioprosthetic valve: final report of the Veterans Affairs randomized trial. J Am Coll Cardiol. 2000;36(4):1152-8.
111. Oxenham H, Bloomfield P, Wheatley DJ, Lee RJ, Cunningham J, Prescott RJ, et al. Twenty year comparison of a Bjork-Shiley mechanical heart valve with porcine bioprostheses. Heart. 2003;89(7):715-21.
112. Rozich JD, Carabello BA, Usher BW, Kratz JM, Bell AE, Zile MR. Mitral valve replacement with and without chordal preservation in patients with chronic mitral regurgitation. Mechanisms for differences in postoperative ejection performance. Circulation. 1992;86(6):1718-26.
113. David TE, Burns RJ, Bacchus CM, Druck MN. Mitral valve replacement for mitral regurgitation with and without preservation of chordae tendineae. J Thorac Cardiovasc Surg. 1984;88(5 Pt 1):718-25.
114. Okita Y, Miki S, Ueda Y, Tahata T, Sakai T, Matsuyama K. Comparative evaluation of left ventricular performance after mitral valve repair or valve replacement with or without chordal preservation. J Heart Valve Dis. 1993;2(2):159-66.
115. Yun KL, Sintek CF, Miller DC, Pfeffer TA, Kochamba GS, Khonsari S, et al. Randomized trial comparing partial versus complete chordal-sparing mitral valve replacement: effects on left ventricular volume and function. J Thorac Cardiovasc Surg. 2002;123(4):707-14.
116. Moss RR, Humphries KH, Gao M, Thompson CR, Abel JG, Fradet G, et al. Outcome of mitral valve repair or replacement: a comparison by propensity score analysis. Circulation. 2003;108 Suppl 1:II90-7.

117. Kouris N, Ikonomidis I, Kontogianni D, Smith P, Nihoyannopoulos P. Mitral valve repair versus replacement for isolated non-ischemic mitral regurgitation in patients with preoperative left ventricular dysfunction. A long-term follow-up echocardiography study. Eur J Echocardiogr. 2005;6(6):435-42.
118. Goldman ME, Mora F, Guarino T, Fuster V, Mindich BP. Mitral valvuloplasty is superior to valve replacement for preservation of left ventricular function: an intraoperative two-dimensional echocardiographic study. J Am Coll Cardiol. 1987;10(3):568-75.
119. Galloway AC, Colvin SB, Baumann FG, Grossi EA, Ribakove GH, Harty S, et al. A comparison of mitral valve reconstruction with mitral valve replacement: Intermediate-term results. The Annals of Thoracic Surgery. 1989;47(5):655-62.
120. Suri RM, Schaff HV, Dearani JA, Sundt TM, 3rd, Daly RC, Mullany CJ, et al. Survival advantage and improved durability of mitral repair for leaflet prolapse subsets in the current era. Ann Thorac Surg. 2006;82(3):819-26.
121. Shuhaiber J, Anderson RJ. Meta-analysis of clinical outcomes following surgical mitral valve repair or replacement. Eur J Cardiothorac Surg. 2007;31(2):267-75.
122. Gogbashian A, Sepic J, Soltesz EG, Nascimben L, Cohn LH. Operative and long-term survival of elderly is significantly improved by mitral valve repair. Am Heart J. 2006;151(6):1325-33.
123. Gillinov AM, Blackstone EH, Nowicki ER, Slisatkorn W, Al-Dossari G, Johnston DR, et al. Valve repair versus valve replacement for degenerative mitral valve disease. J Thorac Cardiovasc Surg. 2008;135(4):885-93, 93 e1-2.
124. Lazam S, Vanoverschelde JL, Tribouilloy C, Grigioni F, Suri RM, Avierinos JF, et al. Twenty-Year Outcome After Mitral Repair Versus Replacement for Severe Degenerative Mitral Regurgitation: Analysis of a Large, Prospective, Multicenter, International Registry. Circulation. 2017;135(5):410-22.
125. Goldstein D, Moskowitz AJ, Gelijns AC, Ailawadi G, Parides MK, Perrault LP, et al. Two-Year Outcomes of Surgical Treatment of Severe Ischemic Mitral Regurgitation. N Engl J Med. 2016;374(4):344-53.
126. Senechal M, MacHaalany J, Bertrand OF, O'Connor K, Parenteau J, Dubois-Senechal IN, et al. Predictors of left ventricular remodeling after surgical repair or replacement for pure severe mitral regurgitation caused by leaflet prolapse. Am J Cardiol. 2013;112(4):567-73.
127. Pandis D, Grapsa J, Athanasiou T, Punjabi P, Nihoyannopoulos P. Left ventricular remodeling and mitral valve surgery: prospective study with real-time 3-dimensional echocardiography and speckle tracking. J Thorac Cardiovasc Surg. 2011;142(3):641-9.
128. Hellawell JL, Margulies KB. Myocardial Reverse Remodeling. Cardiovascular Therapeutics. 2012;30(3):172-81.
129. Konstam MA. Reliability of Ventricular Remodeling as a Surrogate for Use in Conjunction With Clinical Outcomes in Heart Failure. Am J Cardiol. 2005;96(6):867-71.
130. Mohty D, Orszulak TA, Schaff HV, Avierinos JF, Tajik JA, Enriquez-Sarano M. Very long-term survival and durability of mitral valve repair for mitral valve prolapse. Circulation. 2001;104(12 Suppl 1):I1-I7.
131. Ailawadi G, Swenson BR, Girotti ME, Gazoni LM, Peeler BB, Kern JA, et al. Is mitral valve repair superior to replacement in elderly patients? Ann Thorac Surg. 2008;86(1):77-85; discussion 6.
132. Silaschi M, Chaubey S, Aldalati O, Khan H, Uzzaman MM, Singh M, et al. Is Mitral Valve Repair Superior to Mitral Valve Replacement in Elderly Patients? Comparison of Short- and Long-Term Outcomes in a Propensity-Matched Cohort. J Am Heart Assoc. 2016;5(8).
133. Grapsa J, Dawson D, Pandis D, Ntalarizou E, Cheung WS, Efthimiadis I, et al. Mitral valve repair results in better right ventricular remodelling than valve replacement for degenerative mitral regurgitation: a three-dimensional echocardiographic study. Hellenic J Cardiol. 2012;53(4):279-86.

134. Chan V, Elmistekawy E, Ruel M, Hynes M, Mesana TG. How Does Mitral Valve Repair Fail in Patients With Prolapse?-Insights From Longitudinal Echocardiographic Follow-Up. Ann Thorac Surg. 2016;102(5):1459-65.
135. Kim JH, Lee SH, Joo HC, Youn YN, Yoo KJ, Chang BC, et al. Effect of Recurrent Mitral Regurgitation After Mitral Valve Repair in Patients With Degenerative Mitral Regurgitation. Circ J. 2017;82(1):93-101.
136. David TE, David CM, Tsang W, Lafreniere-Roula M, Manlhiot C. Long-Term Results of Mitral Valve Repair for Regurgitation Due to Leaflet Prolapse. J Am Coll Cardiol. 2019;74(8):1044-53.
137. Chikwe J, Toyoda N, Anyanwu AC, Itagaki S, Egorova NN, Boateng P, et al. Relation of Mitral Valve Surgery Volume to Repair Rate, Durability, and Survival. J Am Coll Cardiol. 2017.
138. Mirabel M, Iung B, Baron G, Messika-Zeitoun D, Detaint D, Vanoverschelde JL, et al. What are the characteristics of patients with severe, symptomatic, mitral regurgitation who are denied surgery? Eur Heart J. 2007;28(11):1358-65.
139. Tabata N, Sugiura A, Tsujita K, Nickenig G, Sinning JM. Percutaneous interventions for mitral and tricuspid heart valve diseases. Cardiovasc Interv Ther. 2020;35(1):62-71.
140. Alfieri O, Maisano F, De Bonis M, Stefano PL, Torracca L, Oppizzi M, et al. The double-orifice technique in mitral valve repair: a simple solution for complex problems. J Thorac Cardiovasc Surg. 2001;122(4):674-81.
141. Feldman T, Wasserman HS, Herrmann HC, Gray W, Block PC, Whitlow P, et al. Percutaneous mitral valve repair using the edge-to-edge technique: six-month results of the EVEREST Phase I Clinical Trial. J Am Coll Cardiol. 2005;46(11):2134-40.
142. Praz F, Braun D, Unterhuber M, Spirito A, Orban M, Brugger N, et al. Edge-to-Edge Mitral Valve Repair With Extended Clip Arms: Early Experience From a Multicenter Observational Study. JACC Cardiovasc Interv. 2019;12(14):1356-65.
143. Feldman T, Kar S, Rinaldi M, Fail P, Hermiller J, Smalling R, et al. Percutaneous mitral repair with the MitraClip system: safety and midterm durability in the initial EVEREST (Endovascular Valve Edge-to-Edge REpair Study) cohort. J Am Coll Cardiol. 2009;54(8):686-94.
144. Feldman T, Kar S, Elmariah S, Smart SC, Trento A, Siegel RJ, et al. Randomized Comparison of Percutaneous Repair and Surgery for Mitral Regurgitation: 5-Year Results of EVEREST II. J Am Coll Cardiol. 2015;66(25):2844-54.
145. Grayburn PA, Sannino A, Cohen DJ, Kar S, Lim DS, Mishell JM, et al. Predictors of Clinical Response to Transcatheter Reduction of Secondary Mitral Regurgitation: The COAPT Trial. J Am Coll Cardiol. 2020;76(9):1007-14.
146. Obadia JF, Messika-Zeitoun D, Leurent G, Iung B, Bonnet G, Piriou N, et al. Percutaneous Repair or Medical Treatment for Secondary Mitral Regurgitation. N Engl J Med. 2018;379(24):2297-306.
147. Senni M, Adamo M, Metra M, Alfieri O, Vahanian A. Treatment of functional mitral regurgitation in chronic heart failure: can we get a 'proof of concept' from the MITRA-FR and COAPT trials? Eur J Heart Fail. 2019;21(7):852-61.
148. Praz F, Spargias K, Chrissoheris M, Bullesfeld L, Nickenig G, Deuschl F, et al. Compassionate use of the PASCAL transcatheter mitral valve repair system for patients with severe mitral regurgitation: a multicentre, prospective, observational, first-in-man study. Lancet. 2017;390(10096):773-80.
149. Lim DS, Kar S, Spargias K, Kipperman RM, O'Neill WW, Ng MKC, et al. Transcatheter Valve Repair for Patients With Mitral Regurgitation: 30-Day Results of the CLASP Study. JACC Cardiovasc Interv. 2019;12(14):1369-78.
150. Webb John G, Hensey M, Szerlip M, Schäfer U, Cohen Gideon N, Kar S, et al. 1-Year Outcomes for Transcatheter Repair in Patients With Mitral Regurgitation From the CLASP Study. JACC: Cardiovascular Interventions. 2020;13(20):2344-57.

151. Siontis GC, Praz F, Pilgrim T, Mavridis D, Verma S, Salanti G, et al. Transcatheter aortic valve implantation vs. surgical aortic valve replacement for treatment of severe aortic stenosis: a meta-analysis of randomized trials. Eur Heart J. 2016;37(47):3503-12.
152. Dvir D, Webb J, Brecker S, Bleiziffer S, Hildick-Smith D, Colombo A, et al. Transcatheter aortic valve replacement for degenerative bioprosthetic surgical valves: results from the global valve-in-valve registry. Circulation. 2012;126(19):2335-44.
153. Descoutures F, Himbert D, Maisano F, Casselman F, de Weger A, Bodea O, et al. Transcatheter valve-in-ring implantation after failure of surgical mitral repair. Eur J Cardiothorac Surg. 2013;44(1):e8-15.
154. Cheung A, Webb JG, Barbanti M, Freeman M, Binder RK, Thompson C, et al. 5-year experience with transcatheter transapical mitral valve-in-valve implantation for bioprosthetic valve dysfunction. J Am Coll Cardiol. 2013;61(17):1759-66.
155. Coylewright M, Cabalka AK, Malouf JA, Geske JB, Pollak PM, Suri RM, et al. Percutaneous mitral valve replacement using a transvenous, transseptal approach: transvenous mitral valve replacement. JACC Cardiovasc Interv. 2015;8(6):850-7.
156. Himbert D, Bouleti C, Iung B, Nejjari M, Brochet E, Depoix JP, et al. Transcatheter valve replacement in patients with severe mitral valve disease and annular calcification. J Am Coll Cardiol. 2014;64(23):2557-8.
157. Sondergaard L, De Backer O, Franzen OW, Holme SJ, Ihlemann N, Vejlstrup NG, et al. First-in-Human Case of Transfemoral CardiAQ Mitral Valve Implantation. Circ Cardiovasc Interv. 2015;8(7):e002135.
158. Muller DWM, Farivar RS, Jansz P, Bae R, Walters D, Clarke A, et al. Transcatheter Mitral Valve Replacement for Patients With Symptomatic Mitral Regurgitation: A Global Feasibility Trial. J Am Coll Cardiol. 2017;69(4):381-91.
159. Meredith I, Bapat V, Morriss J, McLean M, Prendergast B. Intrepid transcatheter mitral valve replacement system: technical and product description. EuroIntervention. 2016;12(Y):Y78-80.
160. Webb JG, Murdoch DJ, Boone RH, Moss R, Attinger-Toller A, Blanke P, et al. Percutaneous Transcatheter Mitral Valve Replacement: First-in-Human Experience With a New Transseptal System. J Am Coll Cardiol. 2019;73(11):1239-46.
161. Urena M, Brochet E, Lecomte M, Kerneis C, Carrasco JL, Ghodbane W, et al. Clinical and haemodynamic outcomes of balloon-expandable transcatheter mitral valve implantation: a 7-year experience. Eur Heart J. 2018;39(28):2679-89.
162. Yoon SH, Whisenant BK, Bleiziffer S, Delgado V, Dhoble A, Schofer N, et al. Outcomes of transcatheter mitral valve replacement for degenerated bioprostheses, failed annuloplasty rings, and mitral annular calcification. Eur Heart J. 2019;40(5):441-51.
163. Levine RA, Hung J, Otsuji Y, Messas E, Liel-Cohen N, Nathan N, et al. Mechanistic insights into functional mitral regurgitation. Curr Cardiol Rep. 2002;4(2):125-9.
164. Siminiak T, Wu JC, Haude M, Hoppe UC, Sadowski J, Lipiecki J, et al. Treatment of functional mitral regurgitation by percutaneous annuloplasty: results of the TITAN Trial. Eur J Heart Fail. 2012;14(8):931-8.
165. Lipiecki J, Siminiak T, Sievert H, Muller-Ehmsen J, Degen H, Wu JC, et al. Coronary sinus-based percutaneous annuloplasty as treatment for functional mitral regurgitation: the TITAN II trial. Open Heart. 2016;3(2):e000411.
166. Witte KK, Lipiecki J, Siminiak T, Meredith IT, Malkin CJ, Goldberg SL, et al. The REDUCE FMR Trial: A Randomized Sham-Controlled Study of Percutaneous Mitral Annuloplasty in Functional Mitral Regurgitation. JACC Heart Fail. 2019;7(11):945-55.
167. Rogers JH, Boyd WD, Smith TW, Bolling SF. Transcatheter Mitral Valve Direct Annuloplasty with the Millipede IRIS Ring. Interv Cardiol Clin. 2019;8(3):261-7.
168. Rogers JH, Bolling SF. Transseptal direct complete annuloplasty: early experience. Ann Cardiothorac Surg. 2020.
169. Nickenig G, Hammerstingl C, Schueler R, Topilsky Y, Grayburn PA, Vahanian A, et al. Transcatheter Mitral Annuloplasty in Chronic Functional Mitral Regurgitation: 6-Month

Results With the Cardioband Percutaneous Mitral Repair System. JACC Cardiovasc Interv. 2016;9(19):2039-47.
170. Weber M, Ozturk C, Taramasso M, Pozzoli A, Pfister R, Wosten M, et al. Leaflet edge-to-edge treatment versus direct annuloplasty in patients with functional mitral regurgitation. EuroIntervention. 2019;15(10):912-8.
171. Colli A, Manzan E, Fabio FZ, Sarais C, Pittarello D, Speziali G, et al. TEE-guided transapical beating-heart neochord implantation in mitral regurgitation. JACC Cardiovasc Imaging. 2014;7(3):322-3.
172. Kavakli AS, Ozturk NK, Ayoglu RU, Emmiler M, Ozyurek L, Inanoglu K, et al. Anesthetic Management of Transapical Off-Pump Mitral Valve Repair With NeoChord Implantation. J Cardiothorac Vasc Anesth. 2016;30(6):1587-93.
173. Colli A, Manzan E, Aidietis A, Rucinskas K, Bizzotto E, Besola L, et al. An early European experience with transapical off-pump mitral valve repair with NeoChord implantation. Eur J Cardiothorac Surg. 2018;54(3):460-6.
174. Nielsen SL, Timek TA, Lai DT, Daughters GT, Liang D, Hasenkam JM, et al. Edge-to-edge mitral repair: tension on the approximating suture and leaflet deformation during acute ischemic mitral regurgitation in the ovine heart. Circulation. 2001;104(12 Suppl 1):I29-35.
175. Timek TA, Nielsen SL, Lai DT, Tibayan F, Liang D, Daughters GT, et al. Mitral annular size predicts Alfieri stitch tension in mitral edge-to-edge repair. J Heart Valve Dis. 2004;13(2):165-73.
176. De Bonis M, Lapenna E, Maisano F, Barili F, La Canna G, Buzzatti N, et al. Long-term results (</=18 years) of the edge-to-edge mitral valve repair without annuloplasty in degenerative mitral regurgitation: implications for the percutaneous approach. Circulation. 2014;130(11 Suppl 1):S19-24.
177. Rogers JH, Boyd WD, Smith TWR, Ebner AA, Bolling SF. Combined MitraClip Edge-to-Edge Repair With Millipede IRIS Mitral Annuloplasty. JACC Cardiovasc Interv. 2018;11(3):323-4.
178. Ristalli F, Meucci F, Stolcova M, Valente S, Landi D, Di Mario C. MitraClip Implantation to Treat Early Recurrence of Mitral Regurgitation After Percutaneous Direct Annuloplasty With Cardioband. JACC Cardiovasc Interv. 2018;11(14):1416-7.
179. Gibbons RJ, Balady GJ, Beasley JW, Bricker JT, Duvernoy WF, Froelicher VF, et al. ACC/AHA guidelines for exercise testing: executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Exercise Testing). Circulation. 1997;96(1):345-54.
180. Bruce RA, Blackmon JR, Jones JW, Strait G. Exercising Testing in Adult Normal Subjects and Cardiac Patients. Pediatrics. 1963;32:SUPPL 742-56.
181. Bailey IK, Griffith LS, Rouleau J, Strauss W, Pitt B. Thallium-201 myocardial perfusion imaging at rest and during exercise. Comparative sensitivity to electrocardiography in coronary artery disease. Circulation. 1977;55(1):79-87.
182. Bokhari S, Shahzad A, Bergmann SR. Superiority of exercise myocardial perfusion imaging compared with the exercise ECG in the diagnosis of coronary artery disease. Coronary artery disease. 2008;19(6):399-404.
183. Armstrong WF, O'Donnell J, Dillon JC, McHenry PL, Morris SN, Feigenbaum H. Complementary value of two-dimensional exercise echocardiography to routine treadmill exercise testing. Ann Intern Med. 1986;105(6):829-35.
184. Banerjee A, Newman DR, Van den Bruel A, Heneghan C. Diagnostic accuracy of exercise stress testing for coronary artery disease: a systematic review and meta-analysis of prospective studies. Int J Clin Pract. 2012;66(5):477-92.
185. Jeetley P, Burden L, Senior R. Stress echocardiography is superior to exercise ECG in the risk stratification of patients presenting with acute chest pain with negative Troponin. Eur J Echocardiogr. 2006;7(2):155-64.

186. Kafka H, Leach AJ, Fitzgibbon GM. Exercise echocardiography after coronary artery bypass surgery: correlation with coronary angiography. J Am Coll Cardiol. 1995;25(5):1019-23.
187. Task Force M, Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, et al. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. Eur Heart J. 2013;34(38):2949-3003.
188. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J. 2020;41(3):407-77.
189. Lopez-Mattei JC, Shah DJ. The role of cardiac magnetic resonance in valvular heart disease. Methodist DeBakey cardiovascular journal. 2013;9(3):142-8.
190. Greenwood JP, Maredia N, Younger JF, Brown JM, Nixon J, Everett CC, et al. Cardiovascular magnetic resonance and single-photon emission computed tomography for diagnosis of coronary heart disease (CE-MARC): a prospective trial. Lancet. 2012;379(9814):453-60.
191. Greenwood JP, Herzog BA, Brown JM, Everett CC, Nixon J, Bijsterveld P, et al. Prognostic Value of Cardiovascular Magnetic Resonance and Single-Photon Emission Computed Tomography in Suspected Coronary Heart Disease: Long-Term Follow-up of a Prospective, Diagnostic Accuracy Cohort Study. Ann Intern Med. 2016.
192. Nagel E, Greenwood JP, McCann GP, Bettencourt N, Shah AM, Hussain ST, et al. Magnetic Resonance Perfusion or Fractional Flow Reserve in Coronary Disease. N Engl J Med. 2019;380(25):2418-28.
193. Kramer CM, Barkhausen J, Flamm SD, Kim RJ, Nagel E, Society for Cardiovascular Magnetic Resonance Board of Trustees Task Force on Standardized P. Standardized cardiovascular magnetic resonance (CMR) protocols 2013 update. J Cardiovasc Magn Reson. 2013;15:91.
194. Stout KK, Daniels CJ, Aboulhosn JA, Bozkurt B, Broberg CS, Colman JM, et al. 2018 AHA/ACC Guideline for the Management of Adults With Congenital Heart Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2019;73(12):1494-563.
195. Gusso S, Salvador C, Hofman P, Cutfield W, Baldi JC, Taberner A, et al. Design and testing of an MRI-compatible cycle ergometer for non-invasive cardiac assessments during exercise. Biomedical engineering online. 2012;11:13.
196. Sicari R, Nihoyannopoulos P, Evangelista A, Kasprzak J, Lancellotti P, Poldermans D, et al. Stress echocardiography expert consensus statement: European Association of Echocardiography (EAE) (a registered branch of the ESC). Eur J Echocardiogr. 2008;9(4):415-37.
197. Foster EL, Arnold JW, Jekic M, Bender JA, Balasubramanian V, Thavendiranathan P, et al. MR-compatible treadmill for exercise stress cardiac magnetic resonance imaging. Magn Reson Med. 2012;67(3):880-9.
198. La Gerche A, Claessen G, Van de Bruaene A, Pattyn N, Van Cleemput J, Gewillig M, et al. Cardiac MRI: a new gold standard for ventricular volume quantification during high-intensity exercise. Circ Cardiovasc Imaging. 2013;6(2):329-38.
199. Fischer SE, Wickline SA, Lorenz CH. Novel real-time R-wave detection algorithm based on the vectorcardiogram for accurate gated magnetic resonance acquisitions. Magn Reson Med. 1999;42(2):361-70.
200. Raman SV, Dickerson JA, Jekic M, Foster EL, Pennell ML, McCarthy B, et al. Real-time cine and myocardial perfusion with treadmill exercise stress cardiovascular magnetic resonance in patients referred for stress SPECT. J Cardiovasc Magn Reson. 2010;12:41.
201. Garber CE, Blissmer B, Deschenes MR, Franklin BA, Lamonte MJ, Lee IM, et al. American College of Sports Medicine position stand. Quantity and quality of exercise for

developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. Med Sci Sports Exerc. 2011;43(7):1334-59.
202. Rerkpattanapipat P, Gandhi SK, Darty SN, Williams RT, Davis AD, Mazur W, et al. Feasibility to detect severe coronary artery stenoses with upright treadmill exercise magnetic resonance imaging. Am J Cardiol. 2003;92(5):603-6.
203. Jekic M, Foster EL, Ballinger MR, Raman SV, Simonetti OP. Cardiac function and myocardial perfusion immediately following maximal treadmill exercise inside the MRI room. J Cardiovasc Magn Reson. 2008;10:3.
204. Hecht HS, DeBord L, Sotomayor N, Shaw R, Dunlap R, Ryan C. Supine bicycle stress echocardiography: peak exercise imaging is superior to postexercise imaging. J Am Soc Echocardiogr. 1993;6(3 Pt 1):265-71.
205. Presti CF, Armstrong WF, Feigenbaum H. Comparison of echocardiography at peak exercise and after bicycle exercise in evaluation of patients with known or suspected coronary artery disease. J Am Soc Echocardiogr. 1988;1(2):119-26.
206. Peteiro J, Garrido I, Monserrat L, Aldama G, Calvino R, Castro-Beiras A. Comparison of peak and postexercise treadmill echocardiography with the use of continuous harmonic imaging acquisition. J Am Soc Echocardiogr. 2004;17(10):1044-9.
207. Peteiro J, Fabregas R, Montserrat L, Alvarez N, Castro-Beiras A. Comparison of treadmill exercise echocardiography before and after exercise in the evaluation of patients with known or suspected coronary artery disease. J Am Soc Echocardiogr. 1999;12(12):1073-9.
208. Peteiro J, Monserrat L, Perez R, Vazquez E, Vazquez JM, Castro-Beiras A. Accuracy of peak treadmill exercise echocardiography to detect multivessel coronary artery disease: comparison with post-exercise echocardiography. Eur J Echocardiogr. 2003;4(3):182-90.
209. Peteiro J, Bouzas-Mosquera A, Broullon FJ, Garcia-Campos A, Pazos P, Castro-Beiras A. Prognostic value of peak and post-exercise treadmill exercise echocardiography in patients with known or suspected coronary artery disease. Eur Heart J. 2010;31(2):187-95.
210. Peteiro J, Bouzas-Mosquera A, Estevez R, Pazos P, Pineiro M, Castro-Beiras A. Head-to-head comparison of peak supine bicycle exercise echocardiography and treadmill exercise echocardiography at peak and at post-exercise for the detection of coronary artery disease. J Am Soc Echocardiogr. 2012;25(3):319-26.
211. Lafountain RA, da Silveira JS, Varghese J, Mihai G, Scandling D, Craft J, et al. Cardiopulmonary exercise testing in the MRI environment. Physiol Meas. 2016;37(4):N11-25.
212. Raman SV, Dickerson JA, Mazur W, Wong TC, Schelbert EB, Min JK, et al. Diagnostic Performance of Treadmill Exercise Cardiac Magnetic Resonance: The Prospective, Multicenter Exercise CMR's Accuracy for Cardiovascular Stress Testing (EXACT) Trial. J Am Heart Assoc. 2016;5(8).
213. Thavendiranathan P, Dickerson JA, Scandling D, Balasubramanian V, Pennell ML, Hinton A, et al. Comparison of treadmill exercise stress cardiac MRI to stress echocardiography in healthy volunteers for adequacy of left ventricular endocardial wall visualization: A pilot study. J Magn Reson Imaging. 2014;39(5):1146-52.
214. Sukpraphrute B, Drafts BC, Rerkpattanapipat P, Morgan TM, Kirkman PM, Ntim WO, et al. Prognostic utility of cardiovascular magnetic resonance upright maximal treadmill exercise testing. J Cardiovasc Magn Reson. 2015;17:103.
215. Korosoglou G, Giusca S, Gitsioudis G, Erbel C, Katus HA. Cardiac magnetic resonance and computed tomography angiography for clinical imaging of stable coronary artery disease. Diagnostic classification and risk stratification. Front Physiol. 2014;5:291.
216. Gosselink R, Troosters T, Decramer M. Exercise testing: why, which and how to interpret. Breathe. 2004;1(2):120-9.

217. Badruddin SM, Ahmad A, Mickelson J, Abukhalil J, Winters WL, Nagueh SF, et al. Supine bicycle versus post-treadmill exercise echocardiography in the detection of myocardial ischemia: a randomized single-blind crossover trial. J Am Coll Cardiol. 1999;33(6):1485-90.
218. Ashley EA, Myers J, Froelicher V. Exercise testing in clinical medicine. Lancet. 2000;356(9241):1592-7.
219. Tavel ME, Shaar C. Relation between the electrocardiographic stress test and degree and location of myocardial ischemia. Am J Cardiol. 1999;84(2):119-24.
220. Kligfield P, Lauer MS. Exercise electrocardiogram testing: beyond the ST segment. Circulation. 2006;114(19):2070-82.
221. Jekic M, Ding Y, Dzwonczyk R, Burns P, Raman SV, Simonetti OP. Magnetic field threshold for accurate electrocardiography in the MRI environment. Magn Reson Med. 2010;64(6):1586-91.
222. Fletcher GF, Ades PA, Kligfield P, Arena R, Balady GJ, Bittner VA, et al. Exercise standards for testing and training: a scientific statement from the American Heart Association. Circulation. 2013;128(8):873-934.
223. Pflugi S, Roujol S, Akcakaya M, Kawaji K, Foppa M, Heydari B, et al. Accelerated cardiac MR stress perfusion with radial sampling after physical exercise with an MR-compatible supine bicycle ergometer. Magn Reson Med. 2015;74(2):384-95.
224. Heiberg J, Asschenfeldt B, Maagaard M, Ringgaard S. Dynamic bicycle exercise to assess cardiac output at multiple exercise levels during magnetic resonance imaging. Clinical imaging. 2017;46:102-7.
225. Modesto KM, Rainbird A, Klarich KW, Mahoney DW, Chandrasekaran K, Pellikka PA. Comparison of supine bicycle exercise and treadmill exercise Doppler echocardiography in evaluation of patients with coronary artery disease. Am J Cardiol. 2003;91(10):1245-8.
226. Wicks JR, Sutton JR, Oldridge NB, Jones NL. Comparison of the electrocardiographic changes induced by maximam exercise testing with treadmill and cycle ergometer. Circulation. 1978;57(6):1066-70.
227. Quinn TJ, Smith SW, Vroman NB, Kertzer R, Olney WB. Physiologic responses of cardiac patients to supine, recumbent, and upright cycle ergometry. Arch Phys Med Rehabil. 1995;76(3):257-61.
228. Mohiaddin RH, Gatehouse PD, Firmin DN. Exercise-related changes in aortic flow measured with spiral echo-planar MR velocity mapping. J Magn Reson Imaging. 1995;5(2):159-63.
229. Niezen RA, Doornbos J, van der Wall EE, de Roos A. Measurement of aortic and pulmonary flow with MRI at rest and during physical exercise. J Comput Assist Tomogr. 1998;22(2):194-201.
230. Asschenfeldt B, Heiberg J, Ringgaard S, Maagaard M, Redington A, Hjortdal VE. Impaired cardiac output during exercise in adults operated for ventricular septal defect in childhood: a hitherto unrecognised pathophysiological response. Cardiol Young. 2017;27(8):1591-8.
231. Claessen G, Claus P, Delcroix M, Bogaert J, La Gerche A, Heidbuchel H. Interaction between respiration and right versus left ventricular volumes at rest and during exercise: a real-time cardiac magnetic resonance study. Am J Physiol Heart Circ Physiol. 2014;306(6):H816-24.
232. 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.
233. Holverda S, Gan CT, Marcus JT, Postmus PE, Boonstra A, Vonk-Noordegraaf A. Impaired stroke volume response to exercise in pulmonary arterial hypertension. J Am Coll Cardiol. 2006;47(8):1732-3.

234. La Gerche A, Claessen G, Dymarkowski S, Voigt JU, De Buck F, Vanhees L, et al. Exercise-induced right ventricular dysfunction is associated with ventricular arrhythmias in endurance athletes. Eur Heart J. 2015;36(30):1998-2010.
235. Le TT, Bryant JA, Ting AE, Ho PY, Su B, Teo RC, et al. Assessing exercise cardiac reserve using real-time cardiovascular magnetic resonance. J Cardiovasc Magn Reson. 2017;19(1):7.
236. Pedersen EM, Kozerke S, Ringgaard S, Scheidegger MB, Boesiger P. Quantitative abdominal aortic flow measurements at controlled levels of ergometer exercise. Magn Reson Imaging. 1999;17(4):489-94.
237. Pieles GE, Szantho G, Rodrigues JC, Lawton CB, Stuart AG, Bucciarelli-Ducci C, et al. Adaptations of aortic and pulmonary artery flow parameters measured by phase-contrast magnetic resonance angiography during supine aerobic exercise. Eur J Appl Physiol. 2014;114(5):1013-23.
238. Roest AA, Kunz P, Lamb HJ, Helbing WA, van der Wall EE, de Roos A. Biventricular response to supine physical exercise in young adults assessed with ultrafast magnetic resonance imaging. Am J Cardiol. 2001;87(5):601-5.
239. Roest AA, Lamb HJ, van der Wall EE, Vliegen HW, van den Aardweg JG, Kunz P, et al. Cardiovascular response to physical exercise in adult patients after atrial correction for transposition of the great arteries assessed with magnetic resonance imaging. Heart. 2004;90(6):678-84.
240. Sampath S, Derbyshire JA, Ledesma-Carbayo MJ, McVeigh ER. Imaging left ventricular tissue mechanics and hemodynamics during supine bicycle exercise using a combined tagging and phase-contrast MRI pulse sequence. Magn Reson Med. 2011;65(1):51-9.
241. Schnell F, Claessen G, La Gerche A, Claus P, Bogaert J, Delcroix M, et al. Atrial volume and function during exercise in health and disease. J Cardiovasc Magn Reson. 2017;19(1):104.
242. Weber TF, von Tengg-Kobligk H, Kopp-Schneider A, Ley-Zaporozhan J, Kauczor HU, Ley S. High-resolution phase-contrast MRI of aortic and pulmonary blood flow during rest and physical exercise using a MRI compatible bicycle ergometer. Eur J Radiol. 2011;80(1):103-8.
243. Claessen G, Claus P, Ghysels S, Vermeersch P, Dymarkowski S, A LAG, et al. Right ventricular fatigue developing during endurance exercise: an exercise cardiac magnetic resonance study. Med Sci Sports Exerc. 2014;46(9):1717-26.
244. Claessen G, La Gerche A, Dymarkowski S, Claus P, Delcroix M, Heidbuchel H. Pulmonary vascular and right ventricular reserve in patients with normalized resting hemodynamics after pulmonary endarterectomy. J Am Heart Assoc. 2015;4(3):e001602.
245. Claessen G, La Gerche A, Van De Bruaene A, Claeys M, Willems R, Dymarkowski S, et al. Heart Rate Reserve in Fontan Patients: Chronotropic Incompetence or Hemodynamic Limitation? J Am Heart Assoc. 2019;8(9):e012008.
246. Van De Bruaene A, La Gerche A, Claessen G, De Meester P, Devroe S, Gillijns H, et al. Sildenafil improves exercise hemodynamics in Fontan patients. Circ Cardiovasc Imaging. 2014;7(2):265-73.
247. Van De Bruaene A, Claessen G, La Gerche A, Kung E, Marsden A, De Meester P, et al. Effect of respiration on cardiac filling at rest and during exercise in Fontan patients: A clinical and computational modeling study. Int J Cardiol Heart Vasc. 2015;9:100-8.
248. Helsen F, Claus P, Van De Bruaene A, Claessen G, La Gerche A, De Meester P, et al. Advanced Imaging to Phenotype Patients With a Systemic Right Ventricle. J Am Heart Assoc. 2018;7(20):e009185.
249. Pinto TE, Gusso S, Hofman PL, Derraik JG, Hornung TS, Cutfield WS, et al. Systolic and diastolic abnormalities reduce the cardiac response to exercise in adolescents with type 2 diabetes. Diabetes care. 2014;37(5):1439-46.

250. Steding-Ehrenborg K, Jablonowski R, Arvidsson PM, Carlsson M, Saltin B, Arheden H. Moderate intensity supine exercise causes decreased cardiac volumes and increased outer volume variations: a cardiovascular magnetic resonance study. J Cardiovasc Magn Reson. 2013;15:96.
251. Beaudry RI, Samuel TJ, Wang J, Tucker WJ, Haykowsky MJ, Nelson MD. Exercise cardiac magnetic resonance imaging: a feasibility study and meta-analysis. Am J Physiol Regul Integr Comp Physiol. 2018;315(4):R638-R45.
252. Lurz P, Muthurangu V, Schievano S, Nordmeyer J, Bonhoeffer P, Taylor AM, et al. Feasibility and reproducibility of biventricular volumetric assessment of cardiac function during exercise using real-time radial k-t SENSE magnetic resonance imaging. J Magn Reson Imaging. 2009;29(5):1062-70.
253. Barber NJ, Ako EO, Kowalik GT, Steeden JA, Pandya B, Muthurangu V. MR augmented cardiopulmonary exercise testing-a novel approach to assessing cardiovascular function. Physiol Meas. 2015;36(5):N85-94.
254. Barber NJ, Ako EO, Kowalik GT, Cheang MH, Pandya B, Steeden JA, et al. Magnetic Resonance-Augmented Cardiopulmonary Exercise Testing: Comprehensively Assessing Exercise Intolerance in Children With Cardiovascular Disease. Circ Cardiovasc Imaging. 2016;9(12).
255. Forouzan O, Warczytowa J, Wieben O, Francois CJ, Chesler NC. Non-invasive measurement using cardiovascular magnetic resonance of changes in pulmonary artery stiffness with exercise. J Cardiovasc Magn Reson. 2015;17:109.
256. Gusso S, Pinto TE, Baldi JC, Robinson E, Cutfield WS, Hofman PL. Diastolic function is reduced in adolescents with type 1 diabetes in response to exercise. Diabetes care. 2012;35(10):2089-94.
257. Gusso S, Pinto T, Baldi JC, Derraik JGB, Cutfield WS, Hornung T, et al. Exercise Training Improves but Does Not Normalize Left Ventricular Systolic and Diastolic Function in Adolescents With Type 1 Diabetes. Diabetes care. 2017;40(9):1264-72.
258. Enos JD, Xue H, Kellman P, Hansen M, Cross R. Free-Breathing Mri Evaluation of Cardiac Volume Measurements during in-Scanner Exercise. J Am Coll Cardiol. 2017;69(11):1455-.
259. Poliner LR, Dehmer GJ, Lewis SE, Parkey RW, Blomqvist CG, Willerson JT. Left ventricular performance in normal subjects: a comparison of the responses to exercise in the upright and supine positions. Circulation. 1980;62(3):528-34.
260. Furukawa K, Nishida K, Yamada C, Niki S, Sugihara H, Kohno Y, et al. Left ventricular size and performance during graded supine exercise in normal subjects. Jpn Heart J. 1983;24(4):503-14.
261. Gorlin R, Cohen LS, Elliott WC, Klein MD, Lane FJ. Effect of supine exercise on left ventricular volume and oxygen consumption in man. Circulation. 1965;32(3):361-71.
262. Crawford MH, White DH, Amon KW. Echocardiographic evaluation of left ventricular size and performance during handgrip and supine and upright bicycle exercise. Circulation. 1979;59(6):1188-96.
263. Stein RA, Michielli D, Fox EL, Krasnow N. Continuous ventricular dimensions in man during supine exercise and recovery. An echocardiographic study. Am J Cardiol. 1978;41(4):655-60.
264. Wong DT, Lee KJ, Yoo SJ, Tomlinson G, Grosse-Wortmann L. Changes in systemic and pulmonary blood flow distribution in normal adult volunteers in response to posture and exercise: a phase contrast magnetic resonance imaging study. J Physiol Sci. 2014;64(2):105-12.
265. Wei Z, Whitehead KK, Khiabani RH, Tree M, Tang E, Paridon SM, et al. Respiratory Effects on Fontan Circulation During Rest and Exercise Using Real-Time Cardiac Magnetic Resonance Imaging. Ann Thorac Surg. 2016;101(5):1818-25.

266. Pedersen EM, Stenbog EV, Frund T, Houlind K, Kromann O, Sorensen KE, et al. Flow during exercise in the total cavopulmonary connection measured by magnetic resonance velocity mapping. Heart. 2002;87(6):554-8.
267. Steeden JA, Atkinson D, Taylor AM, Muthurangu V. Assessing vascular response to exercise using a combination of real-time spiral phase contrast MR and noninvasive blood pressure measurements. J Magn Reson Imaging. 2010;31(4):997-1003.
268. Jaijee S, Quinlan M, Tokarczuk P, Clemence M, Howard L, Gibbs JSR, et al. Exercise cardiac MRI unmasks right ventricular dysfunction in acute hypoxia and chronic pulmonary arterial hypertension. Am J Physiol Heart Circ Physiol. 2018;315(4):H950-H7.
269. Cheng CP, Herfkens RJ, Taylor CA, Feinstein JA. Proximal pulmonary artery blood flow characteristics in healthy subjects measured in an upright posture using MRI: the effects of exercise and age. J Magn Reson Imaging. 2005;21(6):752-8.
270. Simonetti OP, Ahmad R. Low-Field Cardiac Magnetic Resonance Imaging: A Compelling Case for Cardiac Magnetic Resonance's Future. Circ Cardiovasc Imaging. 2017;10(6).
271. Garg R, Malhotra V, Kumar A, Dhar U, Tripathi Y. Effect of isometric handgrip exercise training on resting blood pressure in normal healthy adults. J Clin Diagn Res. 2014;8(9):BC08-10.
272. Mortensen KH, Jones A, Steeden JA, Taylor AM, Muthurangu V. Isometric stress in cardiovascular magnetic resonance-a simple and easily replicable method of assessing cardiovascular differences not apparent at rest. European radiology. 2016;26(4):1009-17.
273. Weiss RG, Bottomley PA, Hardy CJ, Gerstenblith G. Regional myocardial metabolism of high-energy phosphates during isometric exercise in patients with coronary artery disease. N Engl J Med. 1990;323(23):1593-600.
274. Conway MA, Bristow JD, Blackledge MJ, Rajagopalan B, Radda GK. Cardiac metabolism during exercise in healthy volunteers measured by 31P magnetic resonance spectroscopy. Br Heart J. 1991;65(1):25-30.
275. Hudsmith LE, Tyler DJ, Emmanuel Y, Petersen SE, Francis JM, Watkins H, et al. (31)P cardiac magnetic resonance spectroscopy during leg exercise at 3 Tesla. Int J Cardiovasc Imaging. 2009;25(8):819-26.
276. Dass S, Cochlin LE, Suttie JJ, Holloway CJ, Rider OJ, Carden L, et al. Exacerbation of cardiac energetic impairment during exercise in hypertrophic cardiomyopathy: a potential mechanism for diastolic dysfunction. Eur Heart J. 2015;36(24):1547-54.
277. Levelt E, Rodgers CT, Clarke WT, Mahmod M, Ariga R, Francis JM, et al. Cardiac energetics, oxygenation, and perfusion during increased workload in patients with type 2 diabetes mellitus. Eur Heart J. 2016;37(46):3461-9.
278. Globits S, Sakuma H, Shimakawa A, Foo TK, Higgins CB. Measurement of coronary blood flow velocity during handgrip exercise using breath-hold velocity encoded cine magnetic resonance imaging. Am J Cardiol. 1997;79(2):234-7.
279. Hays AG, Hirsch GA, Kelle S, Gerstenblith G, Weiss RG, Stuber M. Noninvasive visualization of coronary artery endothelial function in healthy subjects and in patients with coronary artery disease. J Am Coll Cardiol. 2010;56(20):1657-65.
280. Hays AG, Stuber M, Hirsch GA, Yu J, Schar M, Weiss RG, et al. Non-invasive detection of coronary endothelial response to sequential handgrip exercise in coronary artery disease patients and healthy adults. PloS one. 2013;8(3):e58047.
281. Hays AG, Iantorno M, Soleimanifard S, Steinberg A, Schar M, Gerstenblith G, et al. Coronary vasomotor responses to isometric handgrip exercise are primarily mediated by nitric oxide: a noninvasive MRI test of coronary endothelial function. Am J Physiol Heart Circ Physiol. 2015;308(11):H1343-50.
282. Khiabani RH, Whitehead KK, Han D, Restrepo M, Tang E, Bethel J, et al. Exercise capacity in single-ventricle patients after Fontan correlates with haemodynamic energy loss in TCPC. Heart. 2015;101(2):139-43.

283. Tang E, Wei ZA, Whitehead KK, Khiabani RH, Restrepo M, Mirabella L, et al. Effect of Fontan geometry on exercise haemodynamics and its potential implications. Heart. 2017;103(22):1806-12.
284. Habert P, Bentatou Z, Aldebert P, Finas M, Bartoli A, Bal L, et al. Exercise stress CMR reveals reduced aortic distensibility and impaired right-ventricular adaptation to exercise in patients with repaired tetralogy of Fallot. PloS one. 2018;13(12):e0208749.
285. Roest AA, Helbing WA, Kunz P, van den Aardweg JG, Lamb HJ, Vliegen HW, et al. Exercise MR imaging in the assessment of pulmonary regurgitation and biventricular function in patients after tetralogy of fallot repair. Radiology. 2002;223(1):204-11.
286. Yabe T, Mitsunami K, Okada M, Morikawa S, Inubushi T, Kinoshita M. Detection of myocardial ischemia by 31P magnetic resonance spectroscopy during handgrip exercise. Circulation. 1994;89(4):1709-16.
287. Evanochko WT, Buchthal SD, den Hollander JA, Katholi CR, Bourge RC, Benza RL, et al. Cardiac transplant patients response to the (31)P MRS stress test. J Heart Lung Transplant. 2002;21(5):522-9.
288. Leme AM, Salemi VM, Parga JR, Ianni BM, Mady C, Weiss RG, et al. Evaluation of the metabolism of high energy phosphates in patients with Chagas' disease. Arquivos brasileiros de cardiologia. 2010;95(2):264-70.
289. Stern H, Calavrezos L, Meierhofer C, Steinlechner E, Muller J, Hager A, et al. Physical exercise reduces aortic regurgitation: exercise magnetic resonance imaging. JACC Cardiovasc Imaging. 2014;7(3):314-5.
290. Roberts PA, Lin ACW, Cowan BR, Young AA, Stewart R. Comparison of effects of losartan and metoprolol on left ventricular and aortic function at rest and during exercise in chronic aortic regurgitation. Int J Cardiovasc Imaging. 2018;34(4):615-24.
291. Lurz P, Muthurangu V, Schuler PK, Giardini A, Schievano S, Nordmeyer J, et al. Impact of reduction in right ventricular pressure and/or volume overload by percutaneous pulmonary valve implantation on biventricular response to exercise: an exercise stress real-time CMR study. Eur Heart J. 2012;33(19):2434-41.
292. Myerson SG, d'Arcy J, Mohiaddin R, Greenwood JP, Karamitsos TD, Francis JM, et al. Aortic regurgitation quantification using cardiovascular magnetic resonance: association with clinical outcome. Circulation. 2012;126(12):1452-60.
293. Raman Subha V, Hachamovitch R, Scandling D, Mazur W, Kwong Raymond Y, Wong Timothy C, et al. Lower Ischemic Heart Disease Diagnostic Costs With Treadmill Stress CMR Versus SPECT. JACC Cardiovasc Imaging. 2020;13(8):1840-2.
294. Sartoretti T, Reischauer C, Sartoretti E, Binkert C, Najafi A, Sartoretti-Schefer S. Common artefacts encountered on images acquired with combined compressed sensing and SENSE. Insights into Imaging. 2018;9(6):1107-15.
295. Kocaoglu M, Pednekar AS, Wang H, Alsaied T, Taylor MD, Rattan MS. Breath-hold and free-breathing quantitative assessment of biventricular volume and function using compressed SENSE: a clinical validation in children and young adults. J Cardiovasc Magn Reson. 2020;22(1):54.
296. Ma Y, Hou Y, Ma Q, Wang X, Sui S, Wang B. Compressed SENSE single-breath-hold and free-breathing cine imaging for accelerated clinical evaluation of the left ventricle. Clin Radiol. 2019;74(4):325 e9- e17.
297. Kido T, Nakamura M, Watanabe K, Schmidt M, Forman C, Mochizuki T. Assessment of Left Ventricular Function and Mass on Free-Breathing Compressed Sensing Real-Time Cine Imaging. Circ J. 2017;81(10):1463-8.
298. Cho SJ, Choi YJ, Chung SR, Lee JH, Baek JH. High-resolution MRI using compressed sensing-sensitivity encoding (CS-SENSE) for patients with suspected neurovascular compression syndrome: comparison with the conventional SENSE parallel acquisition technique. Clin Radiol. 2019;74(10):817.e9-.e14.

299. Crandon S, Elbaz MSM, Westenberg JJM, van der Geest RJ, Plein S, Garg P. Clinical applications of intra-cardiac four-dimensional flow cardiovascular magnetic resonance: A systematic review. Int J Cardiol. 2017;249:486-93.
300. Macdonald JA, Beshish AG, Corrado PA, Barton GP, Goss KN, Eldridge MW, et al. Feasibility of Cardiovascular Four-dimensional Flow MRI during Exercise in Healthy Participants. Radiol Cardiothorac Imaging. 2020;2(3):e190033.
301. Vanhees L, Lefevre J, Philippaerts R, Martens M, Huygens W, Troosters T, et al. How to assess physical activity? How to assess physical fitness? Eur J Cardiovasc Prev Rehabil. 2005;12(2):102-14.
302. Panton LB, Graves JE, Pollock ML, Garzarella L, Carroll JF, Leggett SH, et al. Relative heart rate, heart rate reserve, and VO2 during submaximal exercise in the elderly. J Gerontol A Biol Sci Med Sci. 1996;51(4):M165-71.
303. Robergs R, Landwehr R. The surprising history of the "HRmax=220-age" equation. J Exerc Physiol Online. 2002;5(2).
304. Fox SM, 3rd, Naughton JP, Haskell WL. Physical activity and the prevention of coronary heart disease. Annals of clinical research. 1971;3(6):404-32.
305. Tanaka H, Monahan KD, Seals DR. Age-predicted maximal heart rate revisited. J Am Coll Cardiol. 2001;37(1):153-6.
306. Machado FA, Denadai BS. Validity of maximum heart rate prediction equations for children and adolescents. Arquivos brasileiros de cardiologia. 2011;97(2):136-40.
307. von Scheidt F, Meier S, Krämer J, Apitz A, Siaplaouras J, Bride P, et al. Heart Rate Response During Treadmill Exercise Test in Children and Adolescents With Congenital Heart Disease. Front Pediatr. 2019;7(65).
308. Gellish RL, Goslin BR, Olson RE, McDonald A, Russi GD, Moudgil VK. Longitudinal modeling of the relationship between age and maximal heart rate. Med Sci Sports Exerc. 2007;39(5):822-9.
309. Gulati M, Shaw LJ, Thisted RA, Black HR, Bairey Merz CN, Arnsdorf MF. Heart rate response to exercise stress testing in asymptomatic women: the st. James women take heart project. Circulation. 2010;122(2):130-7.
310. Karvonen MJ, Kentala E, Mustala O. The effects of training on heart rate; a longitudinal study. Annales medicinae experimentalis et biologiae Fenniae. 1957;35(3):307-15.
311. Byrne NM, Hills A. Relationships between HR and (.)VO(2) in the obese. Med Sci Sports Exerc. 2002;34(9):1419-27.
312. Swain DP. Energy Cost Calculations for Exercise Prescription. Sports Medicine. 2000;30(1):17-22.
313. Davis JA, Convertino VA. A comparison of heart rate methods for predicting endurance training intensity. Med Sci Sports Exerc. 1975;7(4):295-8.
314. Cotsamire DL, Sullivan MJ, Bashore TM, Leier CV. Position as a variable for cardiovascular responses during exercise. Clin Cardiol. 1987;10(3):137-42.
315. Borg GA. Perceived exertion. Exerc Sport Sci Rev. 1974;2:131-53.
316. Chen MJ, Fan X, Moe ST. Criterion-related validity of the Borg ratings of perceived exertion scale in healthy individuals: a meta-analysis. J Sports Sci. 2002;20(11):873-99.
317. Irving BA, Rutkowski J, Brock DW, Davis CK, Barrett EJ, Gaesser GA, et al. Comparison of Borg- and OMNI-RPE as Markers of the Blood Lactate Response to Exercise. Medicine & Science in Sports & Exercise. 2006;38(7).
318. Greenwood JP, Maredia N, Radjenovic A, Brown JM, Nixon J, Farrin AJ, et al. Clinical evaluation of magnetic resonance imaging in coronary heart disease: the CE-MARC study. Trials. 2009;10:62.
319. Petersen SE, Aung N, Sanghvi MM, Zemrak F, Fung K, Paiva JM, et al. Reference ranges for cardiac structure and function using cardiovascular magnetic resonance (CMR) in Caucasians from the UK Biobank population cohort. J Cardiovasc Magn Reson. 2017;19(1):18.

320. Borg G. Psychophysical scaling with applications in physical work and the perception of exertion. Scand J Work Environ Health. 1990;16 Suppl 1:55-8.
321. Nelson RR, Gobel FL, Jorgensen CR, Wang K, Wang Y, Taylor HL. Hemodynamic predictors of myocardial oxygen consumption during static and dynamic exercise. Circulation. 1974;50(6):1179-89.
322. Ruijsink B, Velasco Forte MN, Duong P, Asner L, Pushparajah K, Frigiola A, et al. Synergy in the heart: RV systolic function plays a key role in optimizing LV performance during exercise. Am J Physiol Heart Circ Physiol. 2020;319(3):H642-H50.
323. Otazo R, Kim D, Axel L, Sodickson DK. Combination of compressed sensing and parallel imaging for highly accelerated first-pass cardiac perfusion MRI. Magn Reson Med. 2010;64(3):767-76.
324. Nakamori S, Fahmy A, Jang J, El-Rewaidy H, Neisius U, Berg S, et al. Changes in Myocardial Native T1 and T2 After Exercise Stress: A Noncontrast CMR Pilot Study. JACC Cardiovasc Imaging. 2019.
325. Gelfand EV, Haffajee JA, Hauser TH, Yeon SB, Goepfert L, Kissinger KV, et al. Predictors of preserved left ventricular systolic function after surgery for chronic organic mitral regurgitation: a prospective study. J Heart Valve Dis. 2010;19(1):43-50.
326. McCrum-Gardner E. Which is the correct statistical test to use? Br J Oral Maxillofac Surg. 2008;46(1):38-41.
327. Leung DY, Griffin BP, Snader CE, Luthern L, Thomas JD, Marwick TH. Determinants of Functional Capacity in Chronic Mitral Regurgitation Unassociated With Coronary Artery Disease or Left Ventricular Dysfunction. Am J Cardiol. 1997;79(7):914-20.
328. Haluska BA, Short L, Marwick TH. Relationship of ventricular longitudinal function to contractile reserve in patients with mitral regurgitation. Am Heart J. 2003;146(1):183-8.
329. Lavie CJ, Lam JB, Gibbons RJ. Effects of Exercise on Left Ventricular Volume and Output Changes in Severe Mitral Regurgitation: A Radionuclide Angiographic Study. Chest. 1989;96(5):1086-91.
330. Thadani U, Parker JO. Hemodynamics at rest and during supine and sitting bicycle exercise in normal subjects. Am J Cardiol. 1978;41(1):52-9.
331. Hochreiter C, Niles N, Devereux RB, Kligfield P, Borer JS. Mitral regurgitation: relationship of noninvasive descriptors of right and left ventricular performance to clinical and hemodynamic findings and to prognosis in medically and surgically treated patients. Circulation. 1986;73(5):900-12.
332. Borer JS, Hochreiter C, Rosen S. Right ventricular function in severe non-ischaemic mitral insufficiency. Eur Heart J. 1991;12(suppl_B):22-5.
333. Lebrun F, Lancellotti P, Piérard LA. Quantitation of functional mitral regurgitation during bicycle exercise in patients with heart failure. J Am Coll Cardiol. 2001;38(6):1685-92.
334. Bandera F, Generati G, Pellegrino M, Garatti A, Labate V, Alfonzetti E, et al. Mitral regurgitation in heart failure: insights from CPET combined with exercise echocardiography. Eur Heart J Cardiovasc Imaging. 2017;18(3):296-303.
335. Lancellotti P, Troisfontaines P, Toussaint A-C, Pierard LA. Prognostic Importance of Exercise-Induced Changes in Mitral Regurgitation in Patients With Chronic Ischemic Left Ventricular Dysfunction. Circulation. 2003;108(14):1713-7.
336. Giga V, Ostojic M, Vujisic-Tesic B, Djordjevic-Dikic A, Stepanovic J, Beleslin B, et al. Exercise-induced changes in mitral regurgitation in patients with prior myocardial infarction and left ventricular dysfunction: relation to mitral deformation and left ventricular function and shape. Eur Heart J. 2005;26(18):1860-5.
337. Izumo M, Suzuki K, Moonen M, Kou S, Shimozato T, Hayashi A, et al. Changes in mitral regurgitation and left ventricular geometry during exercise affect exercise capacity in patients with systolic heart failure. Eur J Echocardiogr. 2010;12(1):54-60.
338. Naji P, Griffin Brian P, Barr T, Asfahan F, Gillinov AM, Grimm Richard A, et al. Importance of Exercise Capacity in Predicting Outcomes and Determining Optimal Timing

of Surgery in Significant Primary Mitral Regurgitation. Journal of the American Heart Association.3(5):e001010.
339. Kramer CM, Barkhausen J, Bucciarelli-Ducci C, Flamm SD, Kim RJ, Nagel E. Standardized cardiovascular magnetic resonance imaging (CMR) protocols: 2020 update. J Cardiovasc Magn Reson. 2020;22(1):17.
340. Bertelsen L, Svendsen JH, Køber L, Haugan K, Højberg S, Thomsen C, et al. Flow measurement at the aortic root - impact of location of through-plane phase contrast velocity mapping. J Cardiovasc Magn Reson. 2016;18(1):55.
341. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. Lancet. 2006;368(9540):1005-11.
342. Pomerantzeff PM, Brandão CM, Amato M, Fukushima J, Horta P, Ratti M, et al. [Randomized study comparing mitral valve replacement with and without preservation of mitral ring chordae tendinae papillary continuity]. Arquivos brasileiros de cardiologia. 1993;60(5):321-5.
343. Suri RM, Clavel MA, Schaff HV, Michelena HI, Huebner M, Nishimura RA, et al. Effect of Recurrent Mitral Regurgitation Following Degenerative Mitral Valve Repair: Long-Term Analysis of Competing Outcomes. J Am Coll Cardiol. 2016;67(5):488-98.
344. Crapo RO, Casaburi R, Coates AL, Enright PL, MacIntyre NR, McKay RT, et al. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med. 2002;166(1):111-7.
345. Kawel-Boehm N, Maceira A, Valsangiacomo-Buechel ER, Vogel-Claussen J, Turkbey EB, Williams R, et al. Normal values for cardiovascular magnetic resonance in adults and children. J Cardiovasc Magn Reson. 2015;17(1):29.
346. Maceira AM, Cosín-Sales J, Roughton M, Prasad SK, Pennell DJ. Reference right atrial dimensions and volume estimation by steady state free precession cardiovascular magnetic resonance. J Cardiovasc Magn Reson. 2013;15(1):29.
347. Connelly LM. Fisher's Exact Test. Medsurg Nurs. 2016;25(1):58, 61.
348. Zoghbi WA, Chambers JB, Dumesnil JG, Foster E, Gottdiener JS, Grayburn PA, et al. Recommendations for evaluation of prosthetic valves with echocardiography and doppler ultrasound: a report From the American Society of Echocardiography's Guidelines and Standards Committee and the Task Force on Prosthetic Valves, developed in conjunction with the American College of Cardiology Cardiovascular Imaging Committee, Cardiac Imaging Committee of the American Heart Association, the European Association of Echocardiography, a registered branch of the European Society of Cardiology, the Japanese Society of Echocardiography and the Canadian Society of Echocardiography, endorsed by the American College of Cardiology Foundation, American Heart Association, European Association of Echocardiography, a registered branch of the European Society of Cardiology, the Japanese Society of Echocardiography, and Canadian Society of Echocardiography. J Am Soc Echocardiogr. 2009;22(9):975-1014; quiz 82-4.
349. Mackensen GB, Lee JC, Wang DD, Pearson PJ, Blanke P, Dvir D, et al. Role of Echocardiography in Transcatheter Mitral Valve Replacement in Native Mitral Valves and Mitral Rings. J Am Soc Echocardiogr. 2018;31(4):475-90.
350. Bertrand PB, Levine RA, Isselbacher EM, Vandervoort PM. Fact or Artifact in Two-Dimensional Echocardiography: Avoiding Misdiagnosis and Missed Diagnosis. J Am Soc Echocardiogr. 2016;29(5):381-91.
351. Richau J, Dieringer MA, Traber J, von Knobelsdorff-Brenkenhoff F, Greiser A, Schwenke C, et al. Effects of heart valve prostheses on phase contrast flow measurements in Cardiovascular Magnetic Resonance – a phantom study. J Cardiovasc Magn Reson. 2017;19(1):5.
352. Acker MA, Parides MK, Perrault LP, Moskowitz AJ, Gelijns AC, Voisine P, et al. Mitral-valve repair versus replacement for severe ischemic mitral regurgitation. N Engl J Med. 2014;370(1):23-32.

353. Phillips HR, Levine FH, Carter JE, Boucher CA, Osbakken MD, Okada RD, et al. Mitral valve replacement for isolated mitral regurgitation: analysis of clinical course and late postoperative left ventricular ejection fraction. Am J Cardiol. 1981;48(4):647-54.
354. Irvine T, Li XK, Sahn DJ, Kenny A. Assessment of mitral regurgitation. Heart. 2002;88 Suppl 4:iv11-9.
355. Salis S, Mazzanti VV, Merli G, Salvi L, Tedesco CC, Veglia F, et al. Cardiopulmonary Bypass Duration Is an Independent Predictor of Morbidity and Mortality After Cardiac Surgery. J Cardiothorac Vasc Anesth. 2008;22(6):814-22.
356. Nissinen J, Biancari F, Wistbacka JO, Peltola T, Loponen P, Tarkiainen P, et al. Safe time limits of aortic cross-clamping and cardiopulmonary bypass in adult cardiac surgery. Perfusion. 2009;24(5):297-305.
357. Tay E, Muda N, Yap J, Muller DW, Santoso T, Walters DL, et al. The MitraClip Asia-Pacific registry: Differences in outcomes between functional and degenerative mitral regurgitation. Catheter Cardiovasc Interv. 2016;87(7):E275-81.
358. Chan PH, She HL, Alegria-Barrero E, Moat N, Di Mario C, Franzen O. Real-world experience of MitraClip for treatment of severe mitral regurgitation. Circ J. 2012;76(10):2488-93.
359. Brouwer HJ, Den Heijer MC, Paelinck BP, Debonnaire P, Vanderheyden M, Van De Heyning CM, et al. Left ventricular remodelling patterns after MitraClip implantation in patients with severe mitral valve regurgitation: mechanistic insights and prognostic implications. Eur Heart J Cardiovasc Imaging. 2019;20(3):307-13.
360. Braun D, Lesevic H, Orban M, Michalk F, Barthel P, Hoppe K, et al. Percutaneous edge-to-edge repair of the mitral valve in patients with degenerative versus functional mitral regurgitation. Catheter Cardiovasc Interv. 2014;84(1):137-46.
361. Hamilton-Craig C, Strugnell W, Gaikwad N, Ischenko M, Speranza V, Chan J, et al. Quantitation of mitral regurgitation after percutaneous MitraClip repair: comparison of Doppler echocardiography and cardiac magnetic resonance imaging. Ann Cardiothorac Surg. 2015;4(4):341-51.
362. Krumm P, Zuern CS, Wurster TH, Mangold S, Klumpp BD, Henning A, et al. Cardiac magnetic resonance imaging in patients undergoing percutaneous mitral valve repair with the MitraClip system. Clin Res Cardiol. 2014;103(5):397-404.
363. Radunski UK, Franzen O, Barmeyer A, Lange M, Lund G, Rudolph V, et al. Cardiac remodeling following percutaneous mitral valve repair - initial results assessed by cardiovascular magnetic resonance imaging. Rofo. 2014;186(10):951-8.
364. Lurz P, Serpytis R, Blazek S, Seeburger J, Mangner N, Noack T, et al. Assessment of acute changes in ventricular volumes, function, and strain after interventional edge-to-edge repair of mitral regurgitation using cardiac magnetic resonance imaging. Eur Heart J Cardiovasc Imaging. 2015;16(12):1399-404.
365. Rudolph V, Lubos E, Schluter M, Lubs D, Goldmann B, Knap M, et al. Aetiology of mitral regurgitation differentially affects 2-year adverse outcomes after MitraClip therapy in high-risk patients. Eur J Heart Fail. 2013;15(7):796-807.
366. Maisano F, Franzen O, Baldus S, Schäfer U, Hausleiter J, Butter C, et al. Percutaneous Mitral Valve Interventions in the Real World. J Am Coll Cardiol. 2013;62(12):1052.
367. Maor E, Raphael CE, Panaich SS, Reeder GS, Nishimura RA, Nkomo VT, et al. Acute Changes in Left Atrial Pressure After MitraClip Are Associated With Improvement in 6-Minute Walk Distance. Circ Cardiovasc Interv. 2017;10(4).
368. Velu JF, Hirsch A, Boekholdt SM, Koch KT, Marije Vis M, Nils Planken R, et al. Myocardial fibrosis predicts adverse outcome after MitraClip implantation. Catheter Cardiovasc Interv. 2019;93(6):1146-9.
369. van Riel ACMJ, Boerlage-van Dijk K, de Bruin-Bon RHACM, Araki M, Koch KT, Vis MM, et al. Percutaneous Mitral Valve Repair Preserves Right Ventricular Function. J Am Soc Echocardiogr. 2014;27(10):1098-106.

370. Giannini C, Petronio AS, De Carlo M, Guarracino F, Conte L, Fiorelli F, et al. Integrated reverse left and right ventricular remodelling after MitraClip implantation in functional mitral regurgitation: an echocardiographic study. Eur Heart J Cardiovasc Imaging. 2014;15(1):95-103.
371. Whitlock M, Garg A, Gelow J, Jacobson T, Broberg C. Comparison of Left and Right Atrial Volume by Echocardiography Versus Cardiac Magnetic Resonance Imaging Using the Area-Length Method. Am J Cardiol. 2010;106(9):1345-50.
372. Tsang TSM, Abhayaratna WP, Barnes ME, Miyasaka Y, Gersh BJ, Bailey KR, et al. Prediction of Cardiovascular Outcomes With Left Atrial Size. J Am Coll Cardiol. 2006;47(5):1018.
373. Song BG, On YK, Jeon E-S, Kim D-K, Lee S-C, Park SW, et al. Atrioventricular Reverse Remodeling After Valve Repair for Chronic Severe Mitral Regurgitation: 1-Year Follow-Up. Clinical Cardiology. 2010;33(10):630-7.
374. Desai RR, Vargas Abello LM, Klein AL, Marwick TH, Krasuski RA, Ye Y, et al. Tricuspid regurgitation and right ventricular function after mitral valve surgery with or without concomitant tricuspid valve procedure. J Thorac Cardiovasc Surg. 2013;146(5):1126-32.e10.
375. Shiran A, Sagie A. Tricuspid Regurgitation in Mitral Valve Disease. J Am Coll Cardiol. 2009;53(5):401.
376. Toyama K, Ayabe K, Kar S, Kubo S, Minamishima T, Rader F, et al. Postprocedural Changes of Tricuspid Regurgitation After MitraClip Therapy for Mitral Regurgitation. Am J Cardiol. 2017;120(5):857-61.
377. Patel H, Desai M, Tuzcu EM, Griffin B, Kapadia S. Pulmonary Hypertension in Mitral Regurgitation. Journal of the American Heart Association.3(4):e000748.
378. Dyverfeldt P, Bissell M, Barker AJ, Bolger AF, Carlhäll C-J, Ebbers T, et al. 4D flow cardiovascular magnetic resonance consensus statement. J Cardiovasc Magn Reson. 2015;17(1):72.
379. Fidock B, Barker N, Balasubramanian N, Archer G, Fent G, Al-Mohammad A, et al. A Systematic Review of 4D-Flow MRI Derived Mitral Regurgitation Quantification Methods. Front Cardiovasc Med. 2019;6(103).

Appendix

Ethical approval for Chapters 2 & 3

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

Professor Sven Plein
BHF Professor of Cardiology and Honorary Consultant Cardiologist
University of Leeds
LICAMM
LIGHT building
University of Leeds
LS2 9JT

Email: hra.approval@nhs.net
Research-permissions@wales.nhs.uk

15 June 2018

Dear Professor Plein

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**Advanced Magnetic Resonance Imaging: Optimization of Image Acquisition and Analysis Methods (AMaRI)**
IRAS project ID:	**245109**
REC reference:	**18/YH/0168**
Sponsor	**University of Leeds**

I am pleased to confirm that HRA and Health and Care Research Wales (HCRW) Approval has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

How should I continue to work with participating NHS organisations in England and Wales?
You should now provide a copy of this letter to all participating NHS organisations in England and Wales, as well as any documentation that has been updated as a result of the assessment.

Following the arranging of capacity and capability, participating NHS organisations should **formally confirm** their capacity and capability to undertake the study. How this will be confirmed is detailed in the "*summary of assessment*" section towards the end of this letter.

You should provide, if you have not already done so, detailed instructions to each organisation as to how you will notify them that research activities may commence at site following their confirmation of capacity and capability (e.g. provision by you of a 'green light' email, formal notification following a site initiation visit, activities may commence immediately following confirmation by participating organisation, etc.).

IRAS project ID	245109

It is important that you involve both the research management function (e.g. R&D office) supporting each organisation and the local research team (where there is one) in setting up your study. Contact details of the research management function for each organisation can be accessed here.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?
HRA and HCRW Approval does not apply to NHS/HSC organisations within the devolved administrations of Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report (including this letter) has been sent to the coordinating centre of each participating nation. You should work with the relevant national coordinating functions to ensure any nation specific checks are complete, and with each site so that they are able to give management permission for the study to begin.

Please see IRAS Help for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

How should I work with participating non-NHS organisations?
HRA and HCRW Approval does not apply to non-NHS organisations. You should work with your non-NHS organisations to obtain local agreement in accordance with their procedures.

What are my notification responsibilities during the study?
The document "*After Ethical Review – guidance for sponsors and investigators*", issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

I am a participating NHS organisation in England or Wales. What should I do once I receive this letter?
You should work with the applicant and sponsor to complete any outstanding arrangements so you are able to confirm capacity and capability in line with the information provided in this letter.

The sponsor contact for this application is as follows:

Name: NHS Research Ethics Officer
Email: governance-ethics@leeds.ac.uk

Who should I contact for further information?
Please do not hesitate to contact me for assistance with this application. My contact details are below.

Your IRAS project ID is **245109**. Please quote this on all correspondence.

IRAS project ID	245109

Yours sincerely

Thomas Fairman
HRA Assessor

Email: hra.approval@nhs.net

Copy to: *NHS Research Ethics Office, Leeds University, (Sponsor Contact)*
Ms Anne Gowing, Leeds Teaching Hospitals NHS Trust, (Lead NHS R&D Contact)

IRAS project ID	245109

List of Documents

The final document set assessed and approved by HRA and HCRW Approval is listed below.

Document	*Version*	*Date*
Copies of advertisement materials for research participants [AMaRI recruitment email]	1.0	27 March 2018
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Confirmation of Liability]		21 September 2017
HRA Schedule of Events	1.0	11 April 2018
HRA Statement of Activities	1.0	11 April 2018
IRAS Application Form [IRAS_Form_06042018]		06 April 2018
Laboratory Manual [Laboratory manual]	1.0	01 March 2018
Letter from funder [BHF Programme Grant]		24 May 2016
Letter from sponsor [confirmation of sponsorship]		27 March 2018
Letters of invitation to participant [AMaRI invitation letter]	1.0	27 March 2018
Participant consent form [AMaRI PIS Consent Patients (tracked changes)]	1.1	12 June 2018
Participant consent form [AMaRI PIS Consent Volunteers]	1.1	12 June 2018
Research protocol or project proposal [AMaRI Protocol]	1.1	12 June 2018
Response to Additional Conditions Met		
Summary CV for Chief Investigator (CI) [CV]		01 November 2017

IRAS project ID	245109

Summary of assessment

The following information provides assurance to you, the sponsor and the NHS in England and Wales that the study, as assessed for HRA and HCRW Approval, is compliant with relevant standards. It also provides information and clarification, where appropriate, to participating NHS organisations in England and Wales to assist in assessing, arranging and confirming capacity and capability.

Assessment criteria

Section	Assessment Criteria	Compliant with Standards	Comments
1.1	IRAS application completed correctly	Yes	No comments
2.1	Participant information/consent documents and consent process	Yes	No comment
3.1	Protocol assessment	Yes	No comment
4.1	Allocation of responsibilities and rights are agreed and documented	Yes	The sponsor has submitted the HRA Statement of Activities and intends for this to form the agreement between the sponsor and study sites. The sponsor is not requesting, and does not require any additional contracts with study sites.
4.2	Insurance/indemnity arrangements assessed	Yes	Where applicable, independent contractors (e.g. General Practitioners) should ensure that the professional indemnity provided by their medical defence organisation covers the activities expected of them for this research study
4.3	Financial arrangements assessed	Yes	External study funding has been secured from the British Heart Foundation. Study funding will be provided to sites, as detailed at Schedule 1 of the Statement of Activities.

IRAS project ID	245109

Section	Assessment Criteria	Compliant with Standards	Comments
5.1	Compliance with the Data Protection Act and data security issues assessed	Yes	No comment
5.2	CTIMPS – Arrangements for compliance with the Clinical Trials Regulations assessed	Not Applicable	No comments
5.3	Compliance with any applicable laws or regulations	Yes	No comments
6.1	NHS Research Ethics Committee favourable opinion received for applicable studies	Yes	No comments
6.2	CTIMPS – Clinical Trials Authorisation (CTA) letter received	Not Applicable	No comments
6.3	Devices – MHRA notice of no objection received	Not Applicable	No comments
6.4	Other regulatory approvals and authorisations received	Not Applicable	No comments

Participating NHS Organisations in England and Wales

This provides detail on the types of participating NHS organisations in the study and a statement as to whether the activities at all organisations are the same or different.
All participating NHS organisations will undertake the same study activities. There is therefore only one study site 'type' involved in the research. The Chief Investigator or sponsor should share relevant study documents with participating NHS organisations in England and Wales in order to put arrangements in place to deliver the study. The documents should be sent to both the local study team, where applicable, and the office providing the research management function at the participating organisation. Where applicable, the local LCRN contact should also be copied into this correspondence. If chief investigators, sponsors or principal investigators are asked to complete site level forms for participating NHS organisations in England and Wales which are not provided in IRAS, the HRA or HCRW websites, the chief investigator, sponsor or principal investigator should notify the HRA immediately at hra.approval@nhs.net or HCRW at Research-permissions@wales.nhs.uk. We will work with these organisations to achieve a consistent approach to information provision.

IRAS project ID	245109

Principal Investigator Suitability

This confirms whether the sponsor position on whether a PI, LC or neither should be in place is correct for each type of participating NHS organisation in England and Wales, and the minimum expectations for education, training and experience that PIs should meet (where applicable).
A Principal Investigator should be appointed at study sites. GCP training is not a generic training expectation, in line with the HRA/HCRW/MHRA statement on training expectations.

HR Good Practice Resource Pack Expectations

This confirms the HR Good Practice Resource Pack expectations for the study and the pre-engagement checks that should and should not be undertaken
As a non-commercial study undertaken by local staff, it is unlikely that letters of access or honorary research contracts will be applicable, except where local network staff employed by another Trust (or University) are involved (and then it is likely that arrangements are already in place). Where arrangements are not already in place, network staff (or similar) undertaking any of the research activities listed in A18 or A19 of the IRAS form (except for administration of questionnaires or surveys), would be expected to obtain an honorary research contract from one NHS organisation (if university employed), followed by Letters of Access for subsequent organisations. This would be on the basis of a Research Passport (if university employed) or an NHS to NHS confirmation of pre-engagement checks letter (if NHS employed). These should confirm enhanced DBS checks, including appropriate barred list checks, and occupational health clearance. For research team members only administering questionnaires or surveys, a Letter of Access based on standard DBS checks and occupational health clearance would be appropriate.

Other Information to Aid Study Set-up

This details any other information that may be helpful to sponsors and participating NHS organisations in England to aid study set-up.
The applicant has indicated that they do intend to apply for inclusion on the NIHR CRN Portfolio.

Patient information sheet and consent form – Chapter 2

The Leeds Teaching Hospitals NHS
NHS Trust

UNIVERSITY OF LEEDS

PARTICIPANT INFORMATION SHEET - VOLUNTEERS
Version 1.2 – October 04 2018

AMaRI

Advanced Magnetic Resonance Imaging: Optimization of Image Acquisition and Analysis Methods

Chief Investigator: Professor Sven Plein

Dear Volunteer,

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and your GP if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Purpose of the study

Magnetic Resonance Imaging (MRI) is a test which produces detailed pictures of your internal organs by putting you within a strong magnetic field. MRI allows us to detect abnormalities in many organs in the human body with a very high sensitivity. Importantly, MRI is a safe test and does not use any harmful radiation. It is therefore an increasingly used test in many areas of medicine with over 100,000 MRI scans performed in the NHS every year.

In Leeds, we have an ongoing research programme that aims to continuously improve the way we acquire MRI pictures. This is mostly achieved by making scans shorter, increasing the detail in the image or finding out new information from within the acquired images. These developments are first tested in phantoms (bottles filled with a special liquid) and then need confirmation in volunteers before they can be used in patients.

Why have I been chosen?
This study is looking at up to 400 healthy volunteers. We are also asking 300 patients to participate in the study.

Do I have to take part?
No. It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. We will not access your medical records but instead will ask you to complete a research volunteer form which asks for limited medical information. If you decide to take part you are still free to withdraw at any time and without giving a reason. If there is a possibility that you might be pregnant, you should not take part in the study. Our research team will be happy to discuss any other questions that you may have concerning your suitability for the study, before you decide whether to take part.

What will happen to me if I take part?
Most volunteers will have a single MRI scan. A small group of participants in this study will be asked to undergo up to four MRI scans to allow comparisons between different ways of obtaining MRI pictures. It is entirely up to you how many scans you wish to volunteer for, and

you will remain free to withdraw from the study at any time. All scans will be performed at the Leeds General Infirmary, and will be performed on separate days.

The MRI scan will take approximately 60-90 minutes to complete. You lie in a short 'tunnel', which holds a large magnet. Short bursts of radio waves from the MRI scanner allow images to be created. You will hear periodical loud "banging" noises while we are acquiring the images, so we protect your ears with headphones through which you can listen to the radio or one of your own CDs. We will remain in communication with you throughout the scan.

For most scans we will insert one or two cannulae (small plastic tubes) into veins in your arm. It is likely that we will inject a contrast dye during the scan. Usually people are not aware of the contrast dye injection. At one point we may also inject a medication (Adenosine, or occasionally Dobutamine) into a vein in your arm, which is a drug to increase the blood flow to your heart and other organs. This can cause a brief feeling of warmth, breathlessness or chest discomfort. However all of these feelings, if they occur, usually settle within one or two minutes of the medication being stopped. A doctor will stay in the room with you whilst you are having the medication. In some cases instead of using adenosine we may immerse your hands or feet in cold water for up to 2 minutes to achieve the same increased blood flow to the heart muscle, or we may ask you to use a cycle ergometer, a bicycle which can be used whilst lying down in the scanner.

If we wish to obtain specific images of your heart arteries we will wrap a belt around your abdomen to help improve the quality of the pictures. This is not painful and is a recognized method of doing this type of scan. You may be given a nitrate (GTN) spray under the tongue which helps us to obtaining good images. If your heart beat is quite fast we would give you a beta blocker tablet to reduce your heart rate. Again, these methods are widely used in other centres worldwide and are used in normal clinical work too.

As this study is about improving our scan protocols on an ongoing basis for a period of four years the information we give you has to describe all the different techniques we wish to use in the study overall, but not all the techniques described above will be used during your scan(s). Before you sign the consent form we will discuss with you the specific scanning protocol that we are going to use.

We may ask you for a blood sample (5 to 10 mls. or 1 to 2 teaspoons), which would be taken whilst we insert the cannula in your arm for the contrast, so there are no extra needles involved. Knowing your haematocrit (the volume percentage of red blood cells in the blood) helps us to create specific images which are applicable to clinical practice. We may also test your blood glucose and lipid levels. With your permission we may store serum samples and analyse them at the end of the study for markers of heart function,
We may ask you to come for the scan in a fasted state, or offer to scan you following a meal which we will provide you with, so that we can assess the influence of fed or fasted state on the heart scan assessments.

We may ask you to have an ECG, this is a heart tracing to measure the electrical impulses within the heart. It involves having 10 stickers applied to your chest for 5 minutes.

In the unlikely event of any abnormality we will, with your permission, inform your GP.

Risks and discomforts
Magnetic Resonance Imaging (MRI) is safe and no x-rays or radiation are used for this scan. There are no known risks from this technique. Some people may experience claustrophobia. Our MRI staff will do all that they can to make you feel comfortable during the scan, and will

be monitoring you via a video camera and an audio link. If we are unable to make you feel comfortable in the scanner, we will not go ahead with scanning. You may experience minor bruising or irritation at the site where we place the cannula in your arm. The contrast medication which we use is very safe but, as with any injection, reactions may occur. These include a warm sensation at the injection site, nausea or vomiting and transient skin rash. These effects usually only last for a few minutes. People with a history of allergy are more likely to suffer a more severe reaction, but this is rare (less than 1 in 3000). The department is equipped to cope with allergic reactions if they happen. Adenosine, the medication we use to increase the blood flow to the heart, can cause flushing, breathlessness and chest discomfort. However, all of these feelings usually subside within one or two minutes or even more quickly if the medication is stopped. Nitrates and a beta blocker can cause temporary light headedness. For this reason if these drugs are used you will be kept under observation until the effects have worn off.

Benefits to you
This study is done solely for research purposes and you will not benefit from taking part. Your participation may however benefit patients.

Expenses
We are able to reimburse you £20 per visit as a contribution towards your time and travelling expenses.

Will my taking part be kept confidential?
All information, which is collected about you during the course of the research will be kept strictly confidential. This information will be securely stored at the Cardiac MRI Unit or the Advanced Imaging Centre at Leeds General Infirmary on paper and electronically, under the provisions of the 2018 Data Protection Act. The data collected will be coded and your personal details will be kept separately. If we keep any of your serum samples these will be stored in -80°C freezers in a secure environment, in University of Leeds or Leeds Teaching Hospitals NHS Trust Research laboratories. Stored serum samples will be anonymized and identified only by sample IDs. You will not be identified in any publication that may result from this research.

We will inform your General Practitioner (GP) in the event of an unexpected abnormality being found.

With your permission, your data may also provide a resource for future studies. If any information from this study is used to develop new research, data protection regulations will be observed and strict confidentiality maintained. Your anonymized data and or images may be sent to institutions in the UK, the European Economic Area or outside the EEA. Ethical approval will be obtained for any future studies involving your data. You will not be identified in the results of any future studies.

The University of Leeds is the sponsor for this study based in the United Kingdom. We will be using information from you and/or your medical records in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. The University of Leeds and the Leeds Teaching Hospitals NHS Trust (on behalf of the University of Leeds), will keep identifiable information about you for the purpose of the study for a maximum of 15 years after the study has finished.
Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible.

The Leeds Teaching Hospitals NHS
NHS Trust

UNIVERSITY OF LEEDS

You can find out more about how we use your information at http://www.leeds.ac.uk/secretariat/data_protection.html

The University of Leeds will use your name and contact details to contact you about the research study, and make sure that relevant information about the study is recorded, and to oversee the quality of the study. Individuals from the University of Leeds and regulatory organisations may look at your research records to check the accuracy of the research study. Leeds Teaching Hospitals NHS Trust will pass these details to the University of Leeds along with the information collected from you. The only people in the University of Leeds who will have access to information that identifies you will be people who need to contact you to organize the research or audit the data collection process. The people who analyse the information will not be able to identify you and will not be able to find out your name and contact details. If you give consent to be contacted with regards to participating in future studies the University of Leeds will keep your contact details for up to 3 years.

What will happen to the results of the research study?
When the study is complete the results will be published in a medical journal, but no individual participants will be identified. If you would like a copy of the published results, please ask your doctor.

Indemnity/Compensation
If you are harmed as a direct result of taking part in this study, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds to a legal action. Regardless of this, if you have any cause to complain about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms are available to you.

The research organisation
This is a research project of the Department of Biomedical Imaging Science at the Leeds Institute of Cardiovascular and Metabolic Medicine (LICAMM).

For further information please contact:
Research Nurses
CMR Clinical Research Group
X47 Sunshine Corridor
Leeds General Infirmary
Leeds
LS1 3EX
0113 392 5481 or 392 5504
cmrresearch@leeds.ac.uk

The Leeds Teaching Hospitals NHS
NHS Trust

UNIVERSITY OF LEEDS

CONSENT FORM v 1.2 Oct 04 2018

AMaRI

Advanced Magnetic Resonance Imaging: Optimization of Image Acquisition and Analysis Methods

Chief Investigator: Professor Sven Plein

Patient Number: …….. Date of Birth: ……

Name ……

Please initial boxes

1. I have read the Volunteer Information Sheet dated Oct 04 2018 (Version 1.2) for the above study and I have had the opportunity to ask questions and discuss the research study and I am satisfied with the answers to my questions . ☐
2. I have received enough information about this study. ☐
3. I understand that my participation is voluntary and that I am free to withdraw from the study at any time without giving a reason. ☐
4. I give my consent for my General Practitioner to be informed in the event of any abnormality being discovered. ☐
5. I understand that images collected will be stored on an NHS computer system, and, after my personal details have been removed, may be available to researchers at other institutions in the UK, the EEA, and countries outside the EEA. ☐
6. I understand that some of the blood samples taken from me may be stored and may be analyzed in the future for markers related to heart disease. ☐
7. I understand that relevant sections of my data collected during the study, may be looked at by individuals from the University of Leeds, from regulatory authorities, or from the Leeds Teaching Hospitals NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐
8. If I were to lose capacity, I understand that data already collected will be kept and used for the purposes of the study. ☐
9. I agree to take part in this research study and that the general results of the study will be made available to the medical community most likely through publication in a reputable medical journal. ☐

	Yes	No
10. I am willing to be contacted again in the future to receive information about the publication of this study.	☐	☐
11. I am willing to be contacted again in the future with regard to potentially taking part (without any obligation) in further related	☐	☐

research studies, or attending for further MRI scans.

12. I would like to receive a summary of the final results when they are available ☐

Signature.....

Name (block capitals)..... Date.....

Signature of researcher.....

Name (block capitals).....Date……

1 copy to be given to the patient

1 copy to be filed in notes

1 copy to be retained researcher

The Leeds Teaching Hospitals NHS
NHS Trust

UNIVERSITY OF LEEDS

.....

I am interested in hearing more about this study

(study code: AMaRI)

I give permission for a researcher to contact me by telephone to discuss the study further.

My phone number is.....

Name.....

Address.....

.....

Email address.....

Please return this slip to the research nurse office in the stamped addressed envelope provided.

Thank you.

Chapter 3 patient information and consent form:

The Leeds Teaching Hospitals NHS
NHS Trust

UNIVERSITY OF LEEDS

PARTICIPANT INFORMATION SHEET - PATIENTS
Version 1.2 –October 04 2018
AMaRI

Advanced Magnetic Resonance Imaging: Optimization of Image Acquisition and Analysis Methods

Chief Investigator: Professor Sven Plein

Dear Patient,

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and your GP if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Purpose of the study

Magnetic Resonance Imaging (MRI) is a test which produces detailed pictures of your internal organs by putting you within a strong magnetic field. MRI allows us to detect abnormalities in many organs in the human body with a very high sensitivity. Importantly, MRI is a safe test and does not use any harmful radiation. It is therefore an increasingly used test in many areas of medicine with over 100,000 MRI scans performed in the NHS every year.

In Leeds, we have an ongoing research programme that aims to continuously improve the way we acquire MRI pictures. This is mostly achieved by making scans shorter, increasing the detail in the image or finding out new information from within the acquired images. These developments are first tested in phantoms (bottles filled with a special liquid) and later need confirmation in volunteers and then in patients.

Why have I been chosen?

This study is looking at up to 300 people like you, who may have a range of conditions that are of interest to our research into improving imaging. We are also asking 400 healthy volunteers to participate in the study.

Do I have to take part?

No. It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. This will not affect the standard of care that you receive from the NHS. If there is a possibility that you might be pregnant, you should not take part in the study. Our research team will be happy to discuss any other questions that you may have concerning your suitability for the study, before you decide whether to take part.

What will happen to me if I take part?

Most patients will have a single MRI scan. A small group of participants in this study will be asked to undergo up to four MRI scans to allow comparisons between different ways of obtaining MRI pictures. It is entirely up to you how many scans you wish to volunteer for, and

you will remain free to withdraw from the study at any time. All scans will be performed at the Leeds General Infirmary, and will be performed on separate days.
The MRI scan will take approximately 60 to 90 minutes to complete. You lie in a short 'tunnel', which holds a large magnet. Short bursts of radio waves from the MRI scanner allow images to be created. You will hear periodical loud "banging" noises while we are acquiring the images, so we protect your ears with headphones through which you can listen to the radio or one of your own CDs. We will remain in communication with you throughout the scan.

For most scans we will insert one or two cannulae (small plastic tubes) into veins in your arm. It is likely that we will inject a contrast dye during the scan. Usually people are not aware of the contrast dye injection. At one point we may also inject a medication (Adenosine, or occasionally Dobutamine) into a vein in your arm, which is a drug to increase the blood flow to your heart. This can cause a brief feeling of warmth, breathlessness or chest discomfort. However all of these feelings, if they occur, usually settle within one or two minutes of the medication being stopped. A doctor will stay in the room with you whilst you are having the medication. In some cases instead of using adenosine we may immerse your hands or feet in cold water for up to 2 minutes to achieve the same increased blood flow to the heart muscle, or we may ask you to use a cycle ergometer, a bicycle which can be used whilst lying down in the scanner.

If we wish to obtain specific images of your heart arteries we will wrap a belt around your abdomen to help improve the quality of the pictures. This is not painful and is a recognized method of doing this type of scan. You may be given a nitrate (GTN) spray under the tongue which helps us to obtaining good images. If your heart beat is quite fast we would give you a beta blocker tablet to reduce your heart rate. Again, these methods are widely used in other centres worldwide and are used in normal clinical work too.

As this study is about improving our scan protocols on an ongoing basis for a period of four years the information we give you has to describe all the different techniques we wish to use in the study overall, but not all the techniques described above will be used during your scan(s). Before you sign the consent form we will discuss with you the specific scanning protocol that we are going to use.

We may ask you for a blood sample (5 to 10 mls. or 1 to 2 teaspoons), which would be taken whilst we insert the cannula in your arm for the contrast, so there are no extra needles involved. Knowing your haematocrit (the volume percentage of red blood cells in the blood) helps us to create specific images which are applicable to clinical practice. We may also test your blood glucose and lipid levels. With your permission we may store serum samples and analyse them at the end of the study for markers of heart function.
We may ask you to come for the scan in a fasted state, or offer to scan you following a meal which we will provide you with, so that we can assess the influence of fed or fasted state on the heart scan assessments.

We may ask you to have an ECG, this is a heart tracing to measure the electrical impulses within the heart. It involves having 10 stickers applied to your chest for 5 minutes.

In the unlikely event of any abnormality we will, with your permission, inform your GP.

Risks and discomforts
Magnetic Resonance Imaging (MRI) is safe and no x-rays or radiation are used for this scan. There are no known risks from this technique. Some people may experience claustrophobia. Our MRI staff will do all that they can to make you feel comfortable during the scan, and will be monitoring you via a video camera and an audio link. If we are unable to make

you feel comfortable in the scanner, we will not go ahead with scanning. You may experience minor bruising or irritation at the site where we place the cannula in your arm.The contrast medication which we use is very safe but, as with any injection, reactions may occur. These include a warm sensation at the injection site, nausea or vomiting and transient skin rash. These effects usually only last for a few minutes. People with a history of allergy are more likely to suffer a more severe reaction, but this is rare (less than 1 in 3000). The department is equipped to cope with allergic reactions if they happen. Adenosine, the medication we use to increase the blood flow to the heart, can cause flushing, breathlessness and chest discomfort. However, all of these feelings usually subside within one or two minutes or even more quickly if the medication is stopped. Immersing your hands or feet in cold water is unpleasant, but the effects wear off very quickly. Nitrates and a beta blocker can cause temporary light headedness. For this reason if these drugs are used you will be kept under observation until the effects have worn off.

Benefits to you
This study does not form part of your normal clinical care and is done solely for research purposes. Your participation may however benefit future patients.

Expenses
We will provide reasonable travel expenses should this be necessary for you to attend the MRI scan. We are also happy to arrange transport to the hospital and return you home if needs be.

Will my taking part be kept confidential?
All information, which is collected about you during the course of the research will be kept strictly confidential. This information will be securely stored at the Cardiac MRI Unit at Leeds General Infirmary on paper and electronically, under the provisions of the 2018 Data Protection Act. The data collected will be coded and your personal details will be kept separately. If we keep any of your serum samples these will be stored in -80°C freezers in a secure environment, in University of Leeds or Leeds Teaching Hospitals NHS Trust Research laboratories. Stored serum samples will be anonymized and identified only by sample IDs. You will not be identified in any publication that may result from this research.

We will inform your General Practitioner (GP) in the event of an unexpected abnormality being found.

With your permission, your data may also provide a resource for future studies. If any information from this study is used to develop new research, data protection regulations will be observed and strict confidentiality maintained. Your anonymized data and or images may be sent to institutions in the UK, the European Economic Area or outside the EEA. Ethical approval will be obtained for any future studies involving your data. You will not be identified in the results of any future studies.

The University of Leeds is the sponsor for this study based in the United Kingdom. We will be using information from you and/or your medical records in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. The University of Leeds and the Leeds Teaching Hospitals NHS Trust (on behalf of the University of Leeds), will keep identifiable information about you for the purpose of the study for a maximum of 15 years after the study has finished. Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the

study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible.
You can find out more about how we use your information at http://www.leeds.ac.uk/secretariat/data_protection.html

The University of Leeds will use your name, NHS number and contact details to contact you about the research study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study. Individuals from the University of Leeds and regulatory organisations may look at your medical and research records to check the accuracy of the research study. Leeds Teaching Hospitals NHS Trust will pass these details to the University of Leeds along with the information collected from you and your medical records. The only people in the University of Leeds who will have access to information that identifies you will be people who need to contact you to organize the research or audit the data collection process. The people who analyse the information will not be able to identify you and will not be able to find out your name, NHS number and contact details.

What will happen to the results of the research study?
When the study is complete the results will be published in a medical journal, but no individual participants will be identified. If you would like a copy of the published results, please ask your doctor.

Indemnity/Compensation
If you are harmed as a direct result of taking part in this study, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds to a legal action. Regardless of this, if you have any cause to complain about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms are available to you.

The research organisation
This is a research project of the Department of Biomedical Imaging Science at the Leeds Institute of Cardiovascular and Metabolic Medicine (LICAMM).

For further information please contact:
Research Nurses
CMR Clinical Research Group
X47, Sunshine Corridor
Leeds General Infirmary
Leeds
LS1 3EX
T 0113 392 5481 or 392 5504
cmrresearch@leeds.ac.uk

The Leeds Teaching Hospitals NHS
NHS Trust

UNIVERSITY OF LEEDS

CONSENT FORM v 1.2 October 04 2018

AMaRI

Advanced Magnetic Resonance Imaging: Optimization of Image Acquisition and Analysis Methods
Chief Investigator: Professor Sven Plein

Patient Number: ..... Date of Birth: .....

Patient initials .....

Please initial boxes

1. I have read the Patient Information Sheet dated October 042018 (Version 1.2) for the above study and I have had the opportunity to ask questions and discuss the research study and I am satisfied with the answers to my questions. ☐
2. I have received enough information about this study. ☐
3. I understand that my participation is voluntary and that I am free to withdraw from the study at any time without giving a reason. ☐
4. I give my consent for my General Practitioner to be informed in the event of any abnormality being discovered and that the cardiologist will be informed only if we find any abnormality over and above which is already known. ☐
5. I understand that images collected will be stored on an NHS computer system, and, after my personal details have been removed, may be available to researchers at other institutions in the UK, the EEA, and countries outside the EEA. ☐
6. I understand that some of the blood samples taken from me may be stored and may be analyzed in the future for markers related to heart disease ☐
7. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from the University of Leeds, from regulatory authorities, or from the Leeds Teaching Hospitals NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐
8. If I were to lose capacity, I understand that data already collected will be kept and used for the purposes of the study. ☐
9. I agree to take part in this research study and that the general results of the study will be made available to the medical community most likely through publication in a reputable medical journal. ☐

The Leeds Teaching Hospitals NHS
NHS Trust

UNIVERSITY OF LEEDS

		Yes	No
10.	I am willing to be contacted again in the future to receive information about the publication of this study.	☐	☐
11.	I am willing to be contacted again in the future with regard to potentially taking part (without any obligation) in further related research studies, or attending for further MRI scans.	☐	☐
12.	I would like to receive a summary of the final results when they are available	☐	

Signature.....

Name (block capitals)..... Date.....

Signature of researcher.....

Name (block capitals).....Date……

1 copy to be given to the patient

1 copy to be filed in notes

1 copy to be retained researcher

The Leeds Teaching Hospitals NHS
NHS Trust

UNIVERSITY OF LEEDS

.....

I am interested in hearing more about this study

(study code: AMaRI - patients)

I give permission for a researcher to contact me by telephone to discuss the study further.

My phone number is.....

Name.....

Address.....

.....

Please return this slip to the research nurse office in the stamped addressed envelope provided.

Thank you.

Ethical approval & patient information and consent forms for Chapters 4 & 5

NHS
Health Research Authority
Yorkshire & The Humber - South Yorkshire Research Ethics Committee
Unit 001
Jarrow Business Centre
Rolling Mill Road
Jarrow
Tyne and Wear
NE32 3DT

Telephone: 0191 4283548

24 December 2015

Professor John P Greenwood
Professor of Cardiology, Honorary Consultant Cardiologist
University of Leeds
Division of Biomedical Imaging
Leeds Institute of Cardiovascular and Metabolic Medicine
LIGHT Laboratories
LS2 9JT

Dear Professor Greenwood

Study title:	**Serial change in cardiac reverse remodelling, functional capacity and quality of life following surgical and transcatheter mitral valve repair or replacement for mitral valve disease (pilot study)**
REC reference:	**15/YH/0503**
IRAS project ID:	**184499**

Thank you for your letter of 21st December 2015, 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 the REC Manager, Ms Gillian Mayer, nrescommittee.yorkandhumber-southyorks@nhs.net.

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 contest the need for registration they should contact Catherine Blewett (catherineblewett@nhs.net), the HRA does not, however, expect exceptions to be made. Guidance on where to register is provided within IRAS.

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

Approved documents

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

Document	*Version*	*Date*
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only)		
GP/consultant information sheets or letters	1.0	05 October 2015
Letter from sponsor		
Letters of invitation to participant [invitation letter]	1.0	05 October 2015
Other [PIS and consent controls]	2.0	16 December 2015
Other [PIS and consent repair replacement]	2.0	16 December 2015
Other [Invitation Letter]	2.0	16 December 2015
Other [Information for website]		
Other [Research summary rewritten]		
Other [Response to REC]		18 December 2015
Participant information sheet (PIS)	1.0	05 October 2015
REC Application Form [REC_Form_23102015]		23 October 2015
Research protocol or project proposal	1.0	05 October 2015
Summary CV for Chief Investigator (CI)		23 October 2015
Summary CV for student		

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/

15/YH/0503	Please quote this number on all correspondence

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

Yours sincerely

pp

Dr Ian Woolands
Chair

Email:nrescommittee.yorkandhumber-southyorks@nhs.net

Enclosures: "After ethical review – guidance for researchers"

Copy to: *Faculty Research and Governance Administrator*

Anne Gowing, Leeds Teaching Hospitals NHS Trust

NHS
Health Research Authority
Yorkshire & The Humber - South Yorkshire Research Ethics Committee
NHSBT Newcastle Blood Donor Centre
Holland Drive
Newcastle upon Tyne
NE2 4NQ

Tel: 0207 104 8079

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.

28 February 2019

Ms Petra Bijsterveld
Senior Research Nurse & MRI MRF manager
Division of Biomedical Imaging
LICAMM
University of Leeds

Dear Ms Bijsterveld

Study title:	**Serial change in cardiac reverse remodelling, functional capacity and quality of life following surgical and transcatheter mitral valve repair or replacement for mitral valve disease (pilot study)**
REC reference:	**15/YH/0503**
Amendment number:	**Substantial Amendment 4, 14/01/2019**
Amendment date:	**31 January 2019**
IRAS project ID:	**184499**

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

Summary of Amendment

Submission of this amendment was to seek approval to additionally recruit patients with tricuspid valve disease who are either undergoing transcatheter tricuspid valve intervention, or are under surveillance.
The study documentation was revised including a change of the full study title and the short title.
It was to extend the duration of recruitment to 5 years which would result in an end date of 01/03/2021.
Approval was sought to increase the maximum number of patients to be recruited.
The participant information sheets were amended with the HRA recommended wording on GDPR.
The contact details in the participant information sheets were amended following a change of research fellow.

A covering letter was added to send with the 12 month Quality of Life questionnaire.

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 substantial amendment and noted the protocol stated that tricuspid disease severity could be assessed quantitatively using MRI scanning and would be used to separate significant disease patients from the moderate/mild disease patients in the study. However it was not clear whether patients with single/isolated tricuspid disease or this with tricuspid and additional heart valve disease or both patient types are to be included in the group. Due to the high risk of isolated tricuspid valve surgery, it is the intension to recruit only patients from this group for the TriCinch device group or are patients showing heart valve disease and tricuspid disease also included.

Clarification was sought of the clinical inclusion criteria for patients who were planning to be recruited into the new TriCinch intervention technique group and control group.

It was suggested a flow diagram would be helpful.

It was queried if the TriCinch patients would be subject to any additional clinical risk following recruitment into this group as compared to conventional surgery for repair.

Assurances were sought for the clinical efficacy of the device by applicants, preferably also supported by clinical data for its previous elsewhere.

Assurances were required that all the new clinical data from this study from use of the device would be published in publically accessible journals.

You responded stating the study remained as an observational study only, which this far had recruited patients with mitral valve disease who are undergoing interventions. With the advent of the TriCinch device we wish to extend this study to patients with tricuspid valve disease. We are simply performing MRI scans on patients who are either under surveillance or would be undergoing intervention/surgery. ***Decisions regarding clinical treatment are always made prior to, and completely independently of, the research study in question. These decisions are made by the multidisciplinary clinical team caring for the patient.*** *Use of the TriCinch device is subject to an entirely separate clinical governance process.*

The Sub-Committee apologised for the misunderstanding and raised further queries. For clarity, please supply a summary/copy of or reference to the separate study which outlined the clinical use of the TriCinch device as obtained separately by the applicants or their clinical associates.

Assurances were requested that all new clinical data from the study from the use of the TriCinch device would be published in accessible journals.

You responded with a selection of documents relating to the study 'Clinical Trial Evaluation of the Percutaneous 4Tech TriCinch Coil Tricuspid Valve Repair System'. These included the study protocol, MHRA Approval, REC Approval, HRA Approval, and New Interventional Procedures Group approval of Leeds Teaching Hospitals Trust. The latter form outlined the purpose of the study very well in a reasonably strict way.

You stated new data from the use of the TriCinch device would be published in accessible journals.

The sub-committee reviewed the response and approved the amendment.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
GP/consultant information sheets or letters [GP Information Sheet]	1.1, track change	14 January 2019
Letters of invitation to participant [Invitation Letter]	2.1	14 January 2019
Notice of Substantial Amendment (non-CTIMP)	Substantial Amendment 4, 14/01/2019	31 January 2019
Other [12 month QoL Cover Letter]	1.0	14 January 2019
Other [PIS and Consent Form Controls]	2.3, track change	14 January 2019
Other [PIS and Consent Form Repair Replacement]	2.3, track change	14 January 2019
Other [Protocol]	4	23 February 2018
Other [REC Approval]		16 February 2018
Other [HRA Approval]		21 February 2018
Other [MHRA Approval]		20 February 2018
Other [New Interventional Procedure Proposal Form]		16 April 2018
Research protocol or project proposal [Protocol]	1.4, track change	14 January 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

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/

15/YH/0503: Please quote this number on all correspondence

Yours sincerely
Pp

Dr Max Huxham
Chair

E-mail: nrescommittee.yorkandhumber-southyorks@nhs.net

Enclosures:	*List of names and professions of members who took part in the review*
Copy to:	*Ms Anne Gowing, Leeds Teaching Hospitals NHS Trust*
	Professor John P Greenwood, University of Leeds

Yorkshire & The Humber - South Yorkshire Research Ethics Committee

Attendance at Sub-Committee of the REC meeting via correspondence

Committee Members:

Name	*Profession*	*Present*
Dr Geraldine Boyle	Senior Lecturer	Yes
Dr Max Huxham (Chair)	Retired Scientist	Yes

Also in attendance:

Name	*Position (or reason for attending)*
Miss Donna Bennett	REC Assistant

Leeds Institute of Cardiovascular and Metabolic Medicine

Division of Biomedical Imaging
Leeds General Infirmary
Great George Street
Leeds, LS1 3EX

UNIVERSITY OF LEEDS

MRI-MVR-TVR (pilot study)

'Serial change in cardiac reverse remodelling, functional capacity and quality of life following surgical and transcatheter mitral valve repair or replacement for mitral valve disease or transcatheter tricuspid repair for tricuspid valve disease – a pilot study'

Participant Information Leaflet

Version 2.3 January 14 2019

Chief Investigator: Prof John Greenwood

Dear patient,

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and your GP if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

WHY HAVE I BEEN CHOSEN?

This study is looking at people like you, who have mitral or tricuspid valve disease. We are looking at several groups of patients in this study: patients who are going to have a surgical valve replacement or repair (done by a heart surgeon), patients who are going to have a transcatheter valve replacement, a procedure which replaces the valve without the need for surgery (done by a cardiologist). This second technique is newer and we still need to find out more about the long term results for patients. Finally we will look at patients who are not having treatment at this time (the control group). If and how your valve is going to be replaced has been decided by your doctor and is based purely on your health and symptoms. This study is completely separate from that decision.

WHAT IS THE PURPOSE OF THE STUDY?

Patients have their mitral or tricuspid valve replaced or repaired because their own valve does not work properly, which causes problems with the function of the heart and with the circulation. After the valve has been replaced the heart function and the circulation will normally improve. In this study we want to compare that improvement in the different groups of patients. The study will improve our understanding of the body's response to surgery.

Leeds Institute of Cardiovascular and Metabolic Medicine

Division of Biomedical Imaging
Leeds General Infirmary
Great George Street
Leeds, LS1 3EX

UNIVERSITY OF LEEDS

If you are having your mitral valve replaced we would also like to study the blood vessels in the head. As your doctor will have told you one of the risks of valve replacement is small clots travelling from the heart to the head. It is important for us to find out how often this happens with surgery and with non-surgical replacement, and compare the results.

We will use Magnetic Resonance Imaging (MRI) in this study to look at the head and the heart. MRI does not involve radiation and is therefore very safe. It gives us very good images of the blood vessels and can tell how well the heart is pumping.

DO I HAVE TO TAKE PART?

No, it is entirely up to you to decide whether or not to take part. You do not have to decide straightaway; and you may discuss the study further with a member of the research team over the telephone, or once you come into hospital. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. This will not affect the standard of care you receive. Information collected up to the point of your withdrawal may still be used. In the unlikely event of you losing capacity (being unable to make decisions for yourself) you will be withdrawn from the study by us, but information already collected will be kept and used for the purposes of the study.

WHAT WILL HAPPEN TO ME IF I TAKE PART?

Most participants in this study will have MRI scans of their head and heart at the beginning of the study (before your procedure if you are having your valve replaced or repaired). After the surgery, and before you go home, we will scan your head only, which takes about 10 minutes. At the 6 month study visit we will scan your heart again. If you are having tricuspid valve treatment we will not scan your head. During the scans you lie in a short 'tunnel', which holds a large magnet. Short bursts of radio waves from the MRI scanner allow images to be created. You will hear periodical loud “banging” noises while we are acquiring the images. We will remain in communication with you throughout the scan. If you have normal kidney function then once during each heart scan, we will inject an MRI contrast medication into a vein in your arm. The needle used for this will feel like a sharp scratch. Usually people are not aware of the contrast dye injection. Should your kidneys be impaired then the injection will not be given.

You will also have an echocardiogram (ultrasound scan of the heart) at the beginning of the study and again after 6 months, and at the same time points we will do a 6 minute walk test with you (where we see how far you can walk in 6 minutes).
If you are having tricuspid valve treatment we will also measure your ankles to see if they are swollen.

As part of the study we will ask you to fill out 3 questionnaires which will ask questions about how you feel and how this impacts on your day-to day living. A member of the research team can help you with this if you need assistance. We will ask you to complete these again after 6 and after 12 months.

Finally we will take a blood sample (to measure your kidney function, to check for anaemia and to look at markers of heart strain) from you at each of the two visits. If you are having tricuspid valve treatment we will also measure your liver function. We will use the cannula that we use to give you the MRI contrast dye, so it does not involve any extra needles.

After one year we will follow you up, this will involve us looking at your notes, and we may ring you to enquire how your health is. We will send you the 3 questionnaires in the post or we can complete them over the phone, depending on your preference. We may also contact your GP to obtain up to date contact details if required.

WHAT ARE THE RISKS AND DISCOMFORTS?

Magnetic Resonance Imaging (MRI) is safe and no X-rays or radiation are used for this scan. There are no known risks from this technique. Some patients may experience claustrophobia, although the scan will take place on a new scanner with a bigger 'tunnel' than traditional MRI scanners which many patients find very acceptable. The staff will provide every possible means to reduce this sensation. The scan will be stopped immediately if you do not wish to carry on with it. The contrast medication which we use is very safe but, as with any injection, reactions may occur. These include a warm sensation at the injection site, nausea or vomiting and transient skin rash. These effects usually only last for a few minutes. People with a history of allergy are more likely to suffer a more severe reaction, but this is rare (less than 1 in 3000). The department is equipped to cope with allergic reactions if they happen and medical staff will be on hand to deal with any unforeseen circumstances or problems.

There are no risks from having an echocardiogram. This test is safe and easy and doesn't hurt and you will have had at least one previously. The test uses sound waves that echo against structures in your heart to build up a detailed picture of the heart and allows us to measure how leaky your mitral valve is. It is a similar sort of scan to the ultrasound scan used in pregnancy. You may notice some mild discomfort when the probe is pressed on your chest but there are no known long term side effects known.

Blood samples will be taken to measure your kidney function and check for anaemia. This may cause some mild discomfort and occasionally some bruising. We will typically take 20ml (4 teaspoons) of blood per visit. Blood samples will be stored within the LGI to allow for specialist tests to be performed in one batch.
With your permission your stored sample may be used in future heart related research studies.

BENEFITS TO YOU

There are no particular benefits to you from taking part in this study, other than that you may be helping future patients with the same condition.

EXPENSES

We are able to meet reasonable expenses for costs of travel to and from the hospital for the scans and tests after you have left hospital. Alternatively we can arrange transport by pre-paid taxi for you.

WILL MY TAKING PART BE KEPT CONFIDENTIAL?

All information collected about you during the course of the study will be kept strictly confidential. This information will be securely stored, electronically on the Leeds Teaching Hospitals NHS Trust secure server, on the University of Leeds secure server, and on paper, under the provisions of the 2018 Data Protection Act. The data collected will be coded and your personal details will be kept

separately. You will not be identified in any publication that may result from this research. With your permission, we will inform your GP of your participation in the study. If any unexpected abnormality or condition were found we would inform your GP. If you withdraw consent from further study follow-up, or if you were to become incapacitated, any data collected about you up to that point will remain on file and will be included in the final study analysis.

The University of Leeds is the sponsor for this study based in the United Kingdom. We will be using information from you and/or your medical records in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. Leeds Teaching Hospitals NHS Trust and the University of Leeds will keep identifiable information about you for the purpose of the study for 20 years after the study has finished. Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible. You can find out more about how we use your information by emailing dpo@leeds.ac.uk

Leeds Teaching Hospitals NHS Trust and the University of Leeds will use your name, NHS number, and contact details to contact you about the research study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study. Individuals from the University of Leeds and regulatory organizations may look at your medical and research records to check the accuracy of the research study. The Leeds Teaching Hospitals NHS Trust will pass these details to the University of Leeds along with the information collected from you and/or your medical records. The only people in the University of Leeds who will have access to information that identifies you will be people who need to contact you to or audit the data collection process. The people who analyse the information will not be able to identify you and will not be able to find out your name, NHS number or contact details
When you agree to take part in a research study, the information about your health and care may be provided to researchers running other research studies in this organisation and in other organisations. These organisations may be universities, NHS organisations or companies involved in health and care research in this country or abroad. Your information will only be used by organisations and researchers to conduct research in accordance with the UK Policy Framework for Health and Social Care Research.
This information will not identify you and will not be combined with other information in a way that could identify you. The information will only be used for the purpose of health and care research, and cannot be used to contact you or to affect your care. It will not be used to make decisions about future services available to you, such as insurance.

WHAT WILL HAPPEN IF THERE ARE UNEXPECTED ABNORMALITIES ON MY SCAN?
Occasionally abnormalities that were not expected are picked up on the head and heart scans, blood tests or ultrasound heart scan (echocardiogram). If this is the case we will inform both your treating Consultant and your GP, and they will arrange further investigation if they feel that this is necessary.

WHAT WILL HAPPEN TO THE RESULTS OF THE RESEARCH STUDY?
When the study is complete the results will be published in a medical journal, but no individual patients will be identified. If you would like a copy of the published results, please ask your doctor.

INDEMNITY/COMPENSATION

The Leeds Teaching Hospitals NHS
NHS Trust

UNIVERSITY OF LEEDS

You can find out more about how we use your information at http://www.leeds.ac.uk/secretariat/data_protection.html

The University of Leeds will use your name and contact details to contact you about the research study, and make sure that relevant information about the study is recorded, and to oversee the quality of the study. Individuals from the University of Leeds and regulatory organisations may look at your research records to check the accuracy of the research study. Leeds Teaching Hospitals NHS Trust will pass these details to the University of Leeds along with the information collected from you. The only people in the University of Leeds who will have access to information that identifies you will be people who need to contact you to organize the research or audit the data collection process. The people who analyse the information will not be able to identify you and will not be able to find out your name and contact details. If you give consent to be contacted with regards to participating in future studies the University of Leeds will keep your contact details for up to 3 years.

What will happen to the results of the research study?
When the study is complete the results will be published in a medical journal, but no individual participants will be identified. If you would like a copy of the published results, please ask your doctor.

Indemnity/Compensation
If you are harmed as a direct result of taking part in this study, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds to a legal action. Regardless of this, if you have any cause to complain about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms are available to you.

The research organisation
This is a research project of the Department of Biomedical Imaging Science at the Leeds Institute of Cardiovascular and Metabolic Medicine (LICAMM).

For further information please contact:
Research Nurses
CMR Clinical Research Group
X47 Sunshine Corridor
Leeds General Infirmary
Leeds
LS1 3EX
0113 392 5481 or 392 5504
cmrresearch@leeds.ac.uk

Patient Study Number: …… Date of Birth: ……

Hospital Number: …… Initials: ……..

CONSENT FORM – Version 2.3 January 14 2019 2017– MRI-MVR-TVR

	CI: Prof John Greenwood	Please initial box
1.	I confirm that I have read and understood the information sheet (version 2.3 Ja 14 2019) for the above study and have had the opportunity to ask questions and discuss the research study and I am satisfied with the answers to my questions.	
2.	I understand that sections of any of my medical notes may be looked at by members of the research team and authorised personnel within the Leeds Teaching Hospitals NHS Trust and the University of Leeds, where it is relevant to the research or to assess that appropriate research standards are being maintained within the study. I give permission for these individuals to have access to my records. I understand that the information about me will be held in the strictest confidence and that my results will not be available to a third party.	
3.	I give my consent for my General Practitioner to be informed of my participation in the study, and of any unexpected abnormality if found.	
4.	I understand that images collected will be stored on a computer system, and, after my name and address have been removed, may be available to researchers at other institutions in the UK, the EEA, and countries outside the EEA.	
5.	I understand that my participation is voluntary; and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	
6.	I agree to take part in the study and that the general results of the study will be made available to medical community most likely through publication in a reputable medical journal.	
7.	I understand that information held by the NHS and by my General Practitioner may be used to contact me and provide information about my health status. I give permission for this information to be obtained from NHS records and/or my GP if necessary.	
8.	I am willing to be contacted again in the future with regard to potentially taking part (without any obligation) in further related research studies	
9.	If I were to lose the capacity to make decisions for myself, I understand that data already collected will be kept and used for the purposes of the study.	
10.	I agree to my blood sample being stored and used in other future heart related research.	

Name: (block capitals)	Signature:	Date:
Researcher name: (block capitals)	Signature:	Date: