Cardiovascular Magnetic Resonance Imaging for the Investigation of Patients with Mitral Regurgitation

Pei Gee Chew

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Chapter 1

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Chapter 3

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Chapter 5

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Authorship: PC performed acquisition of data, data analysis and interpretation and drafted the manuscript. PS, CF, PG, KB and JG contributed to the conception and design of the study; whilst AC, SI, and LB were involved in the acquisition and analysis of data. PS, JF, GF, CS and DH reviewed and revised the manuscript. SP, KB, and JP offered intellectual input. All authors read and approved the final manuscript.

Chapter 6

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Publications arising from this work

Papers

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Abstracts

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4. Pei Gee Chew*, Peter P Swoboda, Carrie Ferguson, Pankaj Garg, Said Ibeggazene, Abigail L Cook, Louise AE Brown, James R Foley, Graham J Fent, Sebastian Onciul, David M Higgins, Sven Plein, Karen Birch, John P Greenwood. Assessment of cardiovascular response during continuous exercise using multi-shot, navigated, steady-state free precession cardiovascular magnetic resonance imaging: a pilot study of healthy controls. Heart 2018;104:A46-A47. Shortlisted for 'Best of Best Clinical Abstract-Imaging'. Presented both poster and orally at BCS June 2018, Manchester.

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ABSTRACT

Background

Mitral regurgitation (MR) is the second most frequent valve disease in the developed world and accurate assessment of MR severity and its complications are important. With its excellent accuracy and reproducibility, cardiovascular magnetic resonance (CMR) imaging is an ideal tool to quantitatively assess MR severity and its cardiac remodelling in various clinical settings.

Aims

The aims of the thesis were to **1)** Assess the impact of MR severity on cardiac reverse remodeling and patients' outcome in the TAVI population **2)** Assess the impact of mitral valve (MV) repair versus MV replacement on cardiac reverse remodelling **3)** Evaluate the feasibility and reproducibility of a navigated image acquisition method for biventricular physiological assessment during continuous physical exercise **4)** Evaluate the feasibility of exercise CMR (exCMR) in patients with significant MR

Methods

1) 85 patients undergoing TAVI with CMR pre- and 6m post-TAVI were evaluated **2)** Of 65 patients with significant MR, 37 patients (9 MV repair, 10 MV replacement and 18 medical management) with paired CMR scans at baseline and 6-months were evaluated **3)** 10 healthy volunteers underwent exCMR on two separate occasions using a free-breathing, multi-shot, navigated, balanced steady-state free precession cine pulse sequence **4)** 12 patients with significant degenerative MR underwent navigated exCMR.

Findings

1) Significant MR is common in patients undergoing TAVI and improves in the majority post-procedure. Improvement in MR was not associated with more favourable LV reverse remodelling and baseline MR severity was not associated with mortality **2)** MV surgery leads to positive atrial and left ventricular reverse remodelling. In this small series, MV replacement with chordal preservation has similar cardiac reverse remodelling benefits to MV repair **3)** The navigated exCMR protocol allows simultaneous biventricular physiological assessment during *continuous* exercise. Intra- and inter-observer reproducibility were excellent **4)** The navigated exCMR protocol is feasible in clinical patients with significant MR.

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ABBREVIATIONS

2D	2-dimensional
3D	3-dimensional
ACC	American College of Cardiology
AF	atrial fibrillation
AHA	American Heart Association
AMVL	anterior mitral valve leaflet
ANOVA	analysis of variance
AROA	anatomical regurgitant orifice area
AS	aortic stenosis
ASE	American Society of Echocardiography
AUC	area under the curve
BMI	body mass index
BP	blood pressure
CABG	coronary artery bypass graft
CMR	cardiovascular magnetic resonance
CO	cardiac output
CPET	cardiopulmonary exercise test
CT	computed tomography
CV	coefficient of variation
CW	continuous wave
EACVI	European Association of Cardiovascular Imaging
ECG	electrocardiogram
EDV	end-diastolic volume
EF	ejection fraction
EROA	effective regurgitant orifice area
ESC	European Society of Cardiology
ESV	end systolic volume
exCMR	exercise CMR
FOV	field of view
GLS	global longitudinal strain

HRR	heart rate reserve
IQR	inter-quartile range
LA	left atrium
LGE	late gadolinium enhancement
LV	left ventricle/left ventricular
LVEDP	LV end-diastolic pressure
LVEI	left ventricular ejection index
LVOT	left ventricular outflow tract
MF	myocardial fibrosis
MR	mitral regurgitation
MV	mitral valve
NHYA	New York Heart Association
PAP	pulmonary arterial pressure
PC	phase contrast
PHT	pulmonary arterial hypertension
PISA	proximal isovelocity surface area
PMVL	posterior mitral valve leaflet
PW	pulsed-wave
RF	regurgitant fraction
RHD	right hemi-diaphragm
RV	right ventricle/ right ventricular
RVol	regurgitant volume
SD	standard deviation
SV	stroke volume
TAVI	transcatheter aortic valve implantation
TDI	tissue Doppler imaging
TE	echo time
TFE	turbo field echo
TOE	transoesophageal echocardiogram
TR	repetition time
TTE	transthoracic echocardiogram
VC	vena contracta
VENC	velocity encoded
VTI	velocity-time index

Chapter 1 INTRODUCTION

1.1 BACKGROUND

Mitral regurgitation (MR), a retrograde flow from the left ventricle into the left atrium, is the second most frequent valve disease in Europe after aortic valve stenosis (1,2). Although some patients may remain asymptomatic, severe MR eventually leads to left ventricular (LV) failure, pulmonary hypertension, atrial fibrillation and death(3). The degree of MR is defined by the lesion severity (measured as effective regurgitant orifice area [EROA]) and the resulting volume overload (measured as regurgitant volume [RVol])(1). Patients referred to surgical centres for severe MR, based on echocardiography findings, are often found to have only mild or moderate MR on quantitative evaluation(4). Accurate assessment of MR severity and its complications are important, as it not only determines timing and indication for surgical correction, but also carries significant prognostic implications(3,5).

Traditionally, imaging has focused on assessing mitral valve (MV) morphology, hemodynamic severity, ventricular remodelling and suitability for surgical intervention. Recent innovations in non-invasive imaging have provided insights into the quantification of MR, early detection of LV dysfunction, and advanced prognostic assessment; these are potentially additional factors for determining surgical timing in asymptomatic MR.

1.1.1 Anatomy of the mitral valve

The MV apparatus consists of several components: MV annulus, the anterior and posterior MV leaflets, the chordae, and both anterolateral and posteromedial papillary muscles (6). Dysfunction or altered anatomy of any of these components can lead to MR.

i) The annulus

The MV annulus is a 3D saddle-shaped structure and constitutes the anatomical junction between the LV and the left atrium (LA). It serves as the insertion site for the two leaflets; the anterior (AMVL) and posterior (PMVL) leaflets(7) (Figure 1.1). The quadrangular-shaped PMVL is attached to $^{3}/_{5}$ of the annular circumference and consists of 3 distinct scallops referred to as P1 (anterolateral), P2 (middle), and P3 (posteromedial) scallops (8). Conversely, the AMVL is a semi-circular shaped-structure and attaches to approximately $^{2}/_{5}$ of the annular circumference(8). The three opposing segments of the AMVL are labelled as A1 (anterior), A2 (middle), and A3 (posterior) segments. The leaflets meet at the two commissures: the anterior-lateral and posterior-medial commissures (7). The normally structured MV has a coaptation length of several millimetres to ensure valve competency against normal end-systolic pressure(7).

ii) Chordae

The leaflet suspension system is made up of the chordae tendineae which determines the position and tension on the leaflets during end-systole. Chordae originate from the fibrous heads of the papillary muscles and is classified according to their site of insertion on the respective leaflets. “Primary” chordae insert on the free margin of the leaflets, preventing marginal prolapse and ensuring adequate coaptation. “Secondary chordae” insert on the ventricular surface of the body of the leaflets and has a role in reducing tension on leaflet tissue and therefore prevent leaflet billowing (7). Due to their contribution to the ventricular-valve continuity, these secondary chordae may also play a role in LV shaping and function. “Tertiary chordae” on the other hand, connect the base of the PMVL and mitral annulus to the papillary muscle(7).

iii) Papillary muscles and the left ventricle

Papillary muscle provides chordae to both anterior and posterior MV leaflets. Both papillary muscles (antero-lateral and postero-medial) arise from the area between the apical and middle third of the LV free wall. The anterolateral papillary

muscle is often composed of one body or head, whereas the posteromedial papillary muscle may have two or more heads (7).

1.1.2 Aetiology and mechanism of MR

MR is classified as primary (organic) or secondary (functional) MR. Primary MR is caused by intrinsic valve lesions (i.e. degenerative/prolapse/flail), rheumatic disease or endocarditis(9,10). Secondary MR results from LV remodelling, commonly seen in dilated cardiomyopathy or in ischaemic heart disease(11). The aetiology of MR in industrialised countries is predominantly degenerative (61%), followed by rheumatic (14%) and ischaemic disease (7%) (3,11). The mechanism of MR is classified according to Carpentier's functional classification (Figure 1.1) (12). Surgical correction of MV disease is dependent on both aetiology and mechanism, which affect reparability(1).

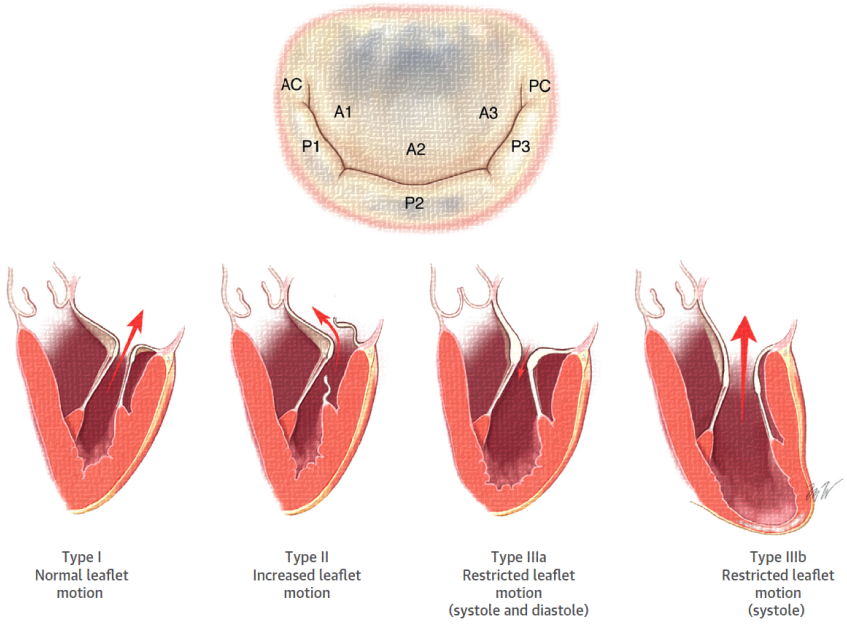

Figure 1.1 Mitral Valve Anatomy and Carpentier classification of mitral regurgitation

Image adapted from Stone et al(13). (Top) Scallops of the posterior MV leaflet is referred to as P1 (anterolateral), P2 (middle), and P3 (posteromedial) scallops. The opposing segments of the anterior leaflet are designated as A1, A2 and A3. AC and PC represent the anterolateral and posteromedial commissures. (Bottom) Leaflet dysfunction (Carpentier Type I, Type II, Type III) is classified on the basis of motion of the free margin of the leaflet in relation to the annular plane.

1.1.2.1 Degenerative mitral valve disease

Degenerative MV disease leads to MV prolapse and has two major phenotypes: a) Barlow's disease and b) Fibroelastic deficiency (3,14). MV prolapse is defined as an abnormal systolic valve movement into the left atrium, ≥2 mm beyond saddle-shaped annular level(15). Prolapse might be of moderate magnitude (leaflet tips remain within the LV i.e. billowing MV) or can be severe (eversion of leaflet tip into the LA caused by ruptured chordae i.e. flail leaflet)(1).

Barlow's disease, typically seen in younger patients (40–60 years old), is characterised by excess leaflet tissue throughout (myxomatous degeneration), chordal thickening and elongation, annular dilatation and a tendency to calcification(7,16). Multiple scallops of both anterior and posterior leaflets prolapse may flail into the LA during systole(17). The dynamics of mitral annulus are impaired in Barlow's disease. This is evidenced by poor contraction and accentuation of the saddle shape during early systole, and further dilatation and flattening of the annulus during late systole(18).

In contrast, fibroelastic deficiency is usually seen in older patients (> 60 years old) and results from the loss of mechanical integrity due to abnormalities of the connective tissue structure. This eventually leads to chordal thinning, elongation, and/or rupture, with classic findings of isolated scallop prolapse and MR of varying severity(8). The associated MR jet is usually eccentric and directed opposite to the prolapsing scallop(16). It is the most common form of primary/organic MV disease of which surgery is required(7). Mitral annulus dynamics are more preserved in this group (18). Interestingly, these different MV annulus dynamics are accompanied by different mitral leaflet dynamics: the leaflet areas of those with fibroelastic deficiencies remained constant throughout systole, whereas the leaflet areas are increased in those with Barlow disease, suggesting larger valvular reserve in these patients. Degenerative MR on the whole is the most reparable form, therefore warranting early and careful assessment(19).

1.1.2.2 Rheumatic MR

Rheumatic disease results in a stiff thickened leaflet with little systolic changes due to fibrotic retraction. Although classic findings are of chordal fusion, chordal shortening and leaflet retraction, they can also be characterised by some degree of commissural fusion(20).

1.1.2.3 Functional MR

Functional (i.e. secondary) MR occurs as a consequence of LV remodelling with displacement of the papillary muscles and tethering of the MV leaflets(21). It is frequently seen in patients with ischaemic or idiopathic dilated cardiomyopathy. Whilst the leaflets are morphologically normal, the MV annulus is usually dilated and deformed(21). Patients with functional MR have a poor prognosis and increasing severity of MR is associated with worse outcome(3).

1.1.2.4 Atrial functional MR

Atrial functional MR describes MR occurring in the context of an isolated mitral annular dilatation where the LV size is normal(22). It is frequently seen in patients with lone AF and in those with heart failure with preserved ejection fraction (22). Inadequate MV leaflet adaptation and coaptation due to annular dilatation leads to a central jet of MR into a dilated LA(23).

1.1.2.5 Ischaemic MR

Ischaemic MR is caused by myocardial ischaemia and/or ventricular remodelling, resulting in papillary muscle displacement with apical tethering and loss of coaptation of the leaflets(24). Whilst the leaflets appear anatomically normal, its mobility is restricted during systole (25). Restoration of myocardial contractile function underlying the papillary muscles might lead to enhanced ventricle–valve interaction to prevent or reduce ischaemic MR(25).

1.1.3 Pathophysiology of MR

Leaflet stretching during ventricular systole promotes the differentiation of valvular interstitial cells into myofibroblasts, inducing leaflet remodelling. The

capacity of the mitral leaflets to undergo remodelling and to compensate for ventricular forces (valve tissue reserve) determines the severity of MR; appropriate remodelling will increase the coaptation surface to reduce MR, whereas inappropriate remodelling will lead to insufficient coaptation with increasing MR(16,18,21). MR results in volume overloaded left ventricle, which responds with progressive atrial and LV dilation and eventually with decreased systolic function and symptoms of heart failure(26,27). Due to these compensatory pathophysiologic mechanisms, structural and functional changes in primary MR may be clinically silent and precede functional limitations and symptoms(28). Symptoms may however occur early on in those who have elevated pulmonary venous pressures or have developed atrial fibrillation (AF) despite a preserved LV function. When symptoms due to reduced cardiac output and/or pulmonary congestion become apparent, serious and sometimes irreversible LV dysfunction has occurred. The subsequent late onset of symptoms might lead to late referral for surgery, although the outcome of medically treated asymptomatic severe primary MR remains unclear(11).

In contrast, secondary (i.e. functional) MR is more complex as ventricular dysfunction predates the regurgitation. Functional MR increases atrial pressure, which leads to pulmonary hypertension and heart failure. With increased atrial pressure and low driving force, functional regurgitation often has low RVol and can be silent(1). Although the degree of MR is defined by lesion severity (EROA) and the yielding volume overload (measured as RVol), it is also affected by the driving force (left-ventricular systolic pressure) and left-atrial compliance(1). The EROA is not necessarily fixed and can be dynamic depending on loading conditions and myocardial contractility. In MV prolapse, the EROA is very dynamic, increasing progressively during systole and is sometimes purely end-systolic. In functional MR, EROA is dynamic during systole, with a large area during short isovolumic contraction and relaxation phases caused by lesser ventricular pressure opposing leaflets(1).

1.1.4 Management of primary MR

The management of patients with MR have been published in both the 2017 American Heart Association/American College of Cardiology (AHA/ACC) focused update (29,30) as well as the 2017 European Society of Cardiology(ESC) valve guidelines(31). MV surgery is indicated for severe MR, usually symptomatic, although surgery is also indicated in selected asymptomatic cases(29,31). The most common indication for MV surgery is symptomatic (i.e. breathlessness or fatigue) severe primary MR, with a LV ejection fraction of >30% (Class 1a). MV surgery is also indicated in symptomatic patients with severe LV dysfunction (LV ejection fraction <30%, and/or LV end-systolic diameter >55mm) refractory to medical therapy when there is low comorbidity(31). In asymptomatic patients with severe MR, surgery is indicated when the LV ejection fraction is ≤60% or the LV end-systolic diameter reaches ≥40mm. Both guidelines states that elective MV repair should be considered if the likelihood of a successful and durable repair without residual MR is >95% with an expected mortality rate of <1% when performed at an experienced centre (Class IIa). Whether an 'early repair' is preferable to a 'watchful waiting' approach in asymptomatic patients with severe MR but without LV dysfunction remains controversial. In these group of patients (LVEF>60% and LVESD<40mm), the 2017 AHA/ACC guidelines have been liberal in recommending MV repair in those with a progressive increase in LV cavity size or decrease in EF on serial imaging studies (Class IIa). An 'early repair' approach prior to the presence of irreversible LV dysfunction is deemed appropriate and may optimise survival and quality of life of patients. On the other hand, the recommendation of ESC in this context is more cautious and only advocates surgical repair in the presence of: a) flail leaflet and LVESD ≥40 mm (Class IIa) or b) if one of the following risk factors is present: indexed LA volume ≥60ml/m^2 and sinus rhythm, or pulmonary hypertension with exercise (systolic pulmonary arterial pressure ≥60 mmHg) (Class IIb).

In light of the relatively sparse data from randomised clinical trials, the recommendations in these international guidelines are only of level B or C and are made based on consensus amongst experts. Over the past decade, new imaging modalities have been introduced, providing new information on the natural history and risk stratification of patients with MR. Persistent dissemination

of updated knowledge in the field is therefore important to favourably influence the outcome of patients with MR.

1.1.4.1 MV Repair versus Replacement

Currently, MV repair is the preferred treatment for patients with primary MR despite the absence of randomised clinical trials comparing these two procedures. The available observational evidence, which dates back a long time, suggests that valve repair is associated with better outcomes than valve replacement (32–35). It is seen to restore life expectancy(5), reduce the risk of heart failure (32,36,37) and mortality (1,35,36). Although MR can recur after repair(38,39), some studies suggests that re-operation rates do not differ after repair compared with replacement(32,35,36).

In the setting of ischaemic MR, one meta-analysis of retrospective studies indicated better short-term and long-term survival after MV repair than after MV replacement(40). Contrary to these findings, Gillinov et al, who retrospectively studied 482 patients, concluded that survival of high-risk patients is similar after MV repair and MV replacement(41). Another study by Goldstein et al(42) randomised 251 patients with severe ischaemic MR to either MV repair or MV replacement. This randomised controlled trial observed no significant between-group difference in cardiac reverse remodelling or survival at 2 years. In fact, the rate of recurrence of moderate or severe MR over 2 years was higher in the repair group than in the replacement group (58% vs 3.8%, $p<0.001$), resulting in more heart failure admissions(42).

The success rates of MV repair in degenerative MR are excellent in patients with a P2 prolapse, but is reduced in cases of extensive disease (≥3 scallops affected), commissural prolapse, severe annulus dilatation (>50 mm) and the presence of extensive calcifications(43). The best outcomes are obtained in asymptomatic patients, operated in experienced centres with low operative mortality (<1%) and high repair rates (≥80–90%)(44). This emphasises the importance of early detection and assessment of MR(1). Whenever the likelihood

of a durable repair by annuloplasty is low, MV replacement with a bio-prosthesis is recommended(43), with complete preservation of the sub- valvular apparatus.

In the early days, there were certain disadvantages associated with the MV replacement that have made it a less favourable strategy. Mechanical prostheses requires life-long anticoagulation and they are associated with an increased risk of thrombosis, bleeding and thromboembolism (26). Furthermore, some studies suggest that LV indices and LV ejection function tend to deteriorate after MV replacement, contributing to morbidity and mortality(26). This appears to relate to the loss of support from the MV apparatus, as chordae and papillary muscles were not preserved with conventional valve replacement techniques. In the last two decades, there has been advancement to the techniques of MV replacement involving the preservation of the sub-valvular apparatus(7,45–47) however there has been little clinical studies performed since their emergence.

1.2 IMAGING MODALITIES

A comprehensive assessment of MR requires evaluation of MV anatomy, MR severity, LV size and systolic function, and assessment of associated features such as presence of pulmonary arterial hypertension (PHT). Echocardiography, which includes both transthoracic (TTE) and transoesophageal (TOE) approaches, has been the cornerstone of assessing MR, providing anatomical and functional information. In most instances, the use of 2-dimensional (2D) and Doppler echocardiographic protocols are sufficient. However, echocardiographic methods have their limitations as they are based on many geometric assumptions, resulting in less accurate quantification of LV function and MR severity. Advanced cross-sectional imaging modalities such as cardiovascular magnetic resonance (CMR) imaging and multi-slice computed tomography (CT) are increasingly useful when echocardiographic imaging is suboptimal and may provide supplementary information in selected patients. Other techniques such as exercise echocardiography, tissue Doppler imaging and speckle-tracking echocardiography can further offer complementary information on prognosis. This chapter summarises the current evidence for state-of-the-art cardiovascular

imaging for the investigation of MR, and highlights the need for greater use of CMR due to its advantages when compared to other imaging modalities.

1.3 Echocardiography

Transthoracic and transoesophageal echocardiography are the mainstay for diagnosis, assessment and serial surveillance. Echocardiographic assessment of MR can determine its aetiology and mechanism, assess its severity as well as the hemodynamic consequences on the LV(1). An integrated and comprehensive assessment of MR requires the following evaluation: a) MV anatomy, b) qualitative findings for MR severity, c) quantitative findings regarding RVol and EROA, d) LV size and function, e) other supportive findings that may determine prognosis or feasibility of successful surgical repair, for example, sub-valvular apparatus or extent of calcification (1), right ventricular function, pulmonary arterial pressure (PAP) and intra-cardiac flows.

1.3.1 Transthoracic echocardiography

1.3.1.1 Assessment of mitral regurgitation severity

Accurate grading of MR severity is essential, as current guidelines only recommend surgical referral when MR is severe by standardised criteria(29,31). Both American Society of Echocardiography (ASE) and ESC guidelines recommend integrating multiple qualitative, semi-quantitative and quantitative echocardiographic parameters when assessing MR severity; although each has their inherent limitations(48,49). Criteria for descriptive and semi-quantitative grading are shown in Table 1.1.

Table 1.1 Qualitative and quantitative parameters used in grading MR severity by Doppler echocardiography; adapted from ASE 2017 (50)

	MR Severity		
	Mild	**Moderate**	**Severe**
Structural			
MV morphology	Non/Mild leaflet abnormality (e.g. mild thickening, calcifications or prolapse, mild tenting)	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 Doppler			
Colour flow jet area	Small, central, narrow, often brief	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	Holo-systolic/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 (>1.2m/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 (may be lower in low flow conditions)
RF (%)	<30	30-39	40-49	≥50

MR, mitral regurgitation; MV, mitral valve; LV, left ventricle; LA, left atria; CW, continuous-wave; VC, vena contracta; AF, atrial fibrillation; EROA, effective regurgitant orifice area; 2D-PISA, 2-dimensional proximal isovelocity surface area; RVol, regurgitant volume

1.3.1.2 Qualitative assessment

Colour Flow Doppler

Although mild MR (a small jet confined to early or late systole with small/absent flow convergence and a narrow vena contracta (VC)) can easily be diagnosed with colour flow imaging, qualitative assessment of larger or more eccentric jets is challenging. Atrial size is inherently linked to atrial pressure and compliance, both of which may themselves affect jet area(51). Eccentric jets commonly project against the atrial wall, exhibit a thin dimension perpendicular to the wall (Coanda effect) and therefore cannot be reliably assessed(51)(Figure 1.2). This technique should therefore not be used for grading MR severity. If more than a small central jet is observed, measurement of the VC and the flow convergence method (proximal isovelocity surface area [PISA]) is recommended (43).

Continuous Wave density jet

The continuous wave (CW) Doppler envelope of the MR signal can provide clues to lesion severity. As the intensity of the Doppler signal is proportionate to the number of scatters (i.e. red blood cells) in the beam, severe MR with large regurgitant volumes will generally produce high intensity Doppler envelopes(51). A dense CW-Doppler signal of the MR jet is consistent with severe MR. Nevertheless, there are several limitations to this method. Firstly, there are no specific criteria for the designation of moderate MR, other than the absence of findings consistent with either mild or severe MR(7). Secondly, interpretation of colour flow patterns is subjective, thus blurring the distinction between moderate and severe(7). As signal density depends on spectral recording of the jet, a central jet well aligned with the ultrasound beam may appear denser than an eccentric jet of much greater severity(50). Thirdly, although specific signs have high positive predictive value, they lack sensitivity for the detection of severe MR(50). These limitations have led to the development of quantitative methods for assessment of MR.

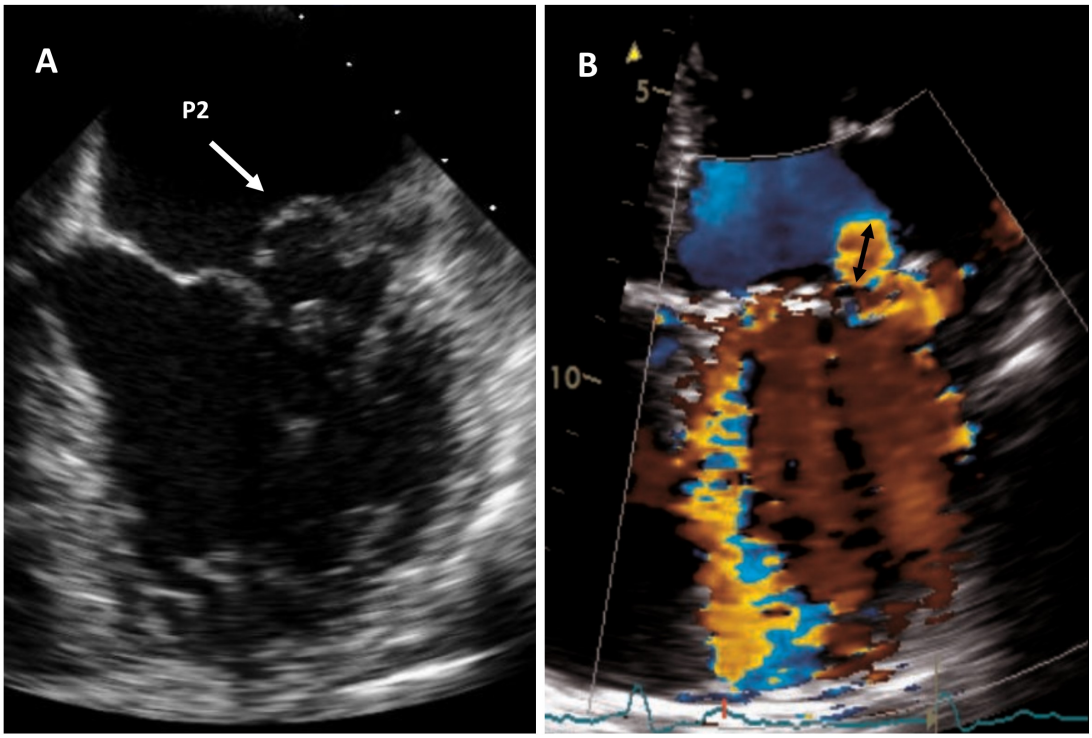

Figure 1.2 Mitral valve prolapse with eccentric jet

(A) Mitral valve posterior leaflet (P2) prolapse seen in transoesophageal echocardiogram. (B) Eccentric, wall–impinging jet of MR with Coanda effect. Although the jet area is small, but the PISA radius (black arrow) is large and signifies the severity of regurgitation.

1.3.1.3 Semi-quantitative assessment

Vena contracta width

The VC, defined as the narrowest portion of the MR regurgitant jet, reflects the regurgitant orifice area and therefore predicts the severity of MR(51). The relation between VC width and EROA has previously been confirmed (52,53), and appears to hold true even in eccentric MR(54). A VC width <3mm is considered as mild MR, whereas a width ≥7mm indicates severe MR. Intermediate values require confirmation by another approach, such as the PISA method. Because of the small values of the width of the VC (usually <1cm), small errors in its measurement may lead to a large percentage error and misclassification of the severity of regurgitation(50).

Pulmonary vein flow/ Mitral inflow

Pulmonary venous systolic flow reversal, a peak mitral E-velocity >1.5 m/s (in the absence of mitral stenosis) and a pulsed-wave Doppler mitral to aortic velocity time integral ratio of >1.4 are additional indicators in favour of severe MR (51).

1.3.1.4 Quantitative assessment

All international guidelines (30,31,48,49) recommend quantitative methods, which measure the RVol, regurgitant fraction (RF) and the EROA, as these appear to have greater accuracy. Quantitation is based on hydrodynamic principles which rely on the non-compressibility of blood and the conservation of mass principle. Flow can be calculated as: flow = [vessel area] x [mean velocity of blood](7).

Geometric assumption concepts are used to measure three parameters indicative of MR severity(7).

1) EROA: The mean area of the systolic regurgitant orifice, a measure of lesion severity
2) Mitral RVol: The volume regurgitated in each systole (ml/beat), a measure of absolute volume overload
3) Mitral RF: The percentage of the total LV stroke volume represented by the RVol, a measure of relative volume overload

In order to derive the above quantitative parameters of MR severity, echocardiography uses these 3 validated methods:

a) Pulsed-wave (PW) Doppler

This quantifies the difference between mitral and aortic stroke volume (SV) with the below equation (51,55).

Equation 1 Echocardiographic quantitation of MR (PW Doppler method)

$$RVol = \text{Mitral}_{SV} - \text{Aortic}_{SV} = [Mitral_{area}\ xVTI_{mitral}] - [Aortic_{area}\ xVTI_{aortic}]$$

$$RF = \frac{RVol}{Mitral_{SV}}\ x\ 100\% = \frac{Rvol}{[Mitral_{area}\ \text{x}\ VTI_{mitral}]}\ x\ 100\%$$

$$EROA = \frac{RVol}{VTI_{mitral\ regurgitation}}$$

RVol is calculated as the difference between mitral and aortic stroke volume(55); RF is noted as the ratio of RVol to mitral stroke volume, and EROA as the ratio of RVol to the regurgitant jet velocity-time index (VTI) (7). In the calculations of stroke volume, both mitral annular area and left ventricular outflow tract (LVOT) are assumed to be circular in geometry(51). Incorrect diameter measurements will result in large errors since the value must be squared to generate the cross-sectional area(51).

b) Volumetric method

This quantitation is based on the difference between LV stroke volume and aortic stroke volume

Equation 2 Echocardiographic quantitation of MR (Volumetric method)

$$RVol = \text{LV}_{SV} - \text{Aortic}_{SV} = [LV_{EDV} - LV_{ESV}] - [Aortic_{area}\ xVTI_{aortic}]$$

$$RF = \frac{RVol}{LV_{sv}}\ x\ 100\% = \frac{RVol}{[LV_{EDV} - LV_{ESV}]}\ x\ 100\%$$

RVol is calculated as the difference between LV stroke volume and aortic stroke volume(50). The mitral SV entity in the previous equation is replaced by LV stroke volume, which was done by tracing end-diastolic and end-systolic LV volumes (7). The potential pitfall of this method is the underestimation of true LV volume (i.e. due to foreshortening or unclear endocardial borders) therefore underestimating regurgitation severity(50). The use of 3-dimensional (3D) echocardiography may help improve the accuracy of LV volume assessment(50).

c) PISA

This method focuses on the flow convergence proximal to the regurgitant orifice as observed with colour-flow imaging, where PISA radius of the convergence zone can be derived. Flow through the convergence zone is presumed to be equivalent to the flow through the regurgitant orifice.

Equation 3 Echocardiographic quantitation of MR (PISA method)

Flow through the convergence zone (i.e.EROA)

$$=[Area\ of\ flow\ x\ Aliaising\ velocity]$$

$$= [2\pi r^2\ x\ Aliaising\ velocity]$$

$$EROA = \frac{[2\pi r^2\ x\ Aliaising\ velocity]}{Peak\ MR_{velocity}}$$

$$RVol = \ EROA\ x\ VTI_{Mitral\ regurgitation}$$

$$= \frac{[2\pi r^2\ x\ Aliaising\ velocity]}{Peak\ MR_{velocity}}\ x\ VTI_{Mitral\ regurgitation}$$

PISA is best imaged in the apical 4-chamber view (or the parasternal views in AMVL prolapse) with a reduced Nyquist limit (15–40 m/s) to obtain a hemispheric iso-velocity area(7,11). The use of CW-Doppler of the MR jet allows calculation of the EROA and the RVol(7,11). Despite its objectiveness, there are again some limitations associated with this method. Since the PISA calculation provides an instantaneous peak flow rate, the EROA calculated by this approach may not be equivalent to the average regurgitant orifice throughout the regurgitant phase(50). Additionally, there are assumptions that the valvular plane from which the regurgitant orifice arises is planar and that the flow convergence is homogeneous, although this is not always the case. In cases where the regurgitant orifice is non-circular, as frequently is seen in functional MR (crescent shape), the PISA shape is no longer hemispheric(50). Application of the standard PISA formula to such an elliptical orifice will lead predictably to flow

underestimation(50) (Figure 1.3). 3D colour-flow would provide a better assessment of the PISA surface, although with additional limitations of lower spatial and temporal resolution(50). The advantages and limitations of each echocardiographic parameter used to quantify MR severity are summarised in Table 1.2.

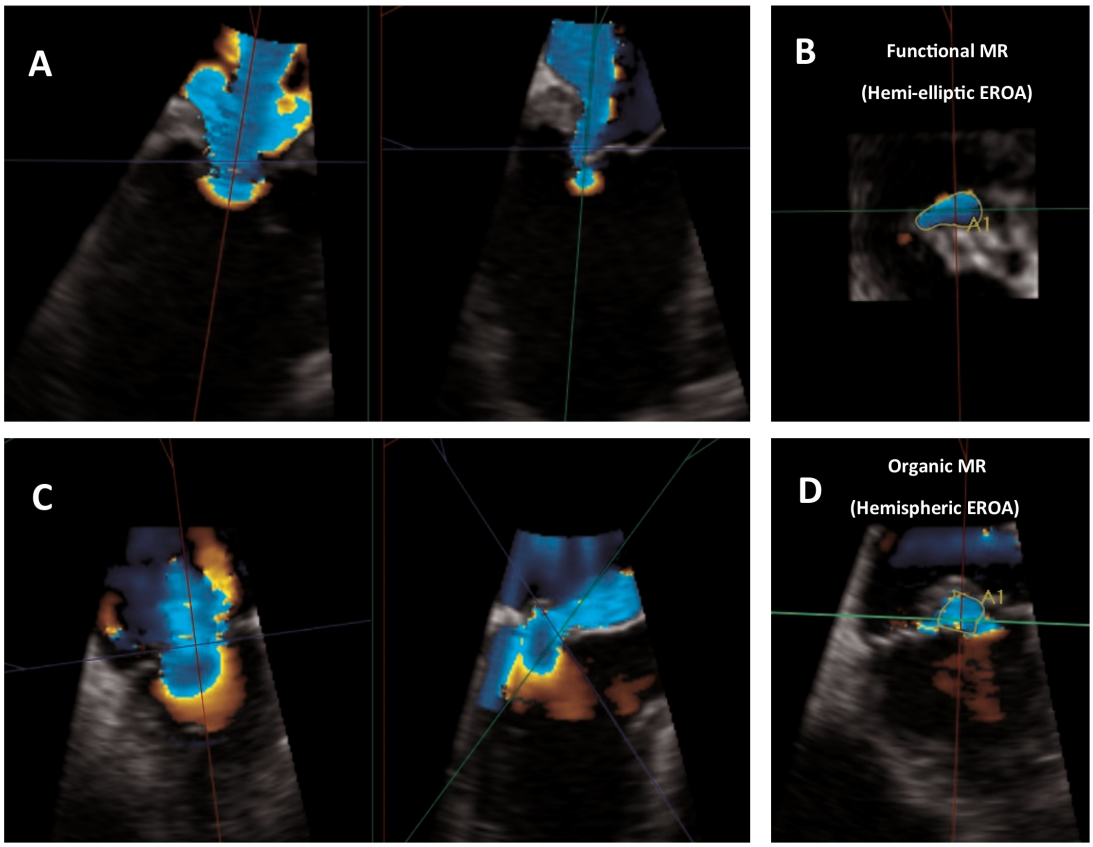

Figure 1.3 Two cases showing evaluation and quantitation of VC area with 3D echocardiography and multi-planar reconstruction

(A-B) A case of functional (secondary) MR with non-hemispheric PISA and elliptical VC area. (C-D) A case of organic (primary) MR with hemispheric PISA and circular VC area. VC, vena contracta; 3D, 3-dimensional; MR, mitral regurgitation; PISA, proximal isovelocity surface area.

Table 1.2 The roles and limitations of echocardiographic parameters used in the assessment of MR(50,51,56,57)

Qualitative		
Colour flow Doppler	• Rapid visual assessment	• Influenced by the cause of MR and jet eccentricity • Jet area affected by atrial pressure and compliance
CW Doppler: Density of MR regurgitant jet	• Simple visual assessment	• Perfectly central jets may appear denser than eccentric jets of higher severity • Density is gain dependent
Quantitative		
2D-PISA	• Rapid qualitative assessment • Absence of proximal flow convergence usually a sign of mild MR	• High inter-observer variability Less accurate for multiple jets and eccentric jets • Non-hemispheric shape (i.e. functional MR) • Non-holosystolic MR (overestimation of RVol) • Dynamic nature of the orifice
2D-VC width	• Good at separating mild from severe MR • Less dependent on technical factors	• Multiple jets; Eccentric jets • Elliptical orifice shape in functional MR (underestimates MR) • Non-holosystolic MR (overestimation of RVol)
EROA, RVol, and RF	• Rapid quantitative assessment • Shown to predict outcomes in degenerative and functional MR	• Multiple jets; Eccentric jets • Markedly crescent-shaped orifices • Small errors in radius measurement can lead to substantial errors in EROA due to squaring of error

MR, mitral regurgitation; CW, continuous-wave; 2D, 2-dimensional; PISA, proximal isovelocity surface area; RVol, regurgitant volume; VC, vena contracta; EROA, effective regurgitant orifice area; RF regurgitant fraction

EROA – 2D PISA

As described above, quantification of the EROA can be performed either by the PW-Doppler method or by using the PISA method (58,59); for which the latter is less time-consuming. EROA is a powerful predictor of outcomes in patients with severe MR. An EROA of ≥40mm^2 (in asymptomatic organic MR) or a EROA of ≥20mm^2 (in ischaemic MR) is associated with an increased risk of all-cause mortality, cardiac mortality and cardiac events(1,5). Although MR is classically holosystolic, patients with MV prolapse often have no MR in early systole, with a relatively large EROA limited to mid- or late systole. Compared with patients with holosystolic MR, those with late systolic MR yield lower MR volume, despite similar EROA and jet areas(60). In such patients, RVol has been shown to be superior to EROA in predicting cardiac death, admission for congestive heart failure, or new-onset atrial fibrillation(60). On the other hand, patients with secondary MR often exhibit a biphasic pattern of MR, with an initial EROA peak in early systole, a decline in mid-systole, and a second peak in late systole and during isovolumic relaxation(61,62). Occasionally, transient MR limited to early systole is seen, particularly with bundle branch block. Thus, duration and timing of MR should be carefully evaluated. EROA to grade MR severity should therefore only be used if adjusted for the duration of MR, where feasible. Volumetric methods for assessing MR would forgo the above limitations and are preferred in non-holosystolic MR(48).

Mitral Regurgitation Volume/ Fraction

Mild primary MR is defined as an RVol <30ml, whereas severe primary MR is defined as a RVol ≥60ml(5). Regurgitant volume may be a useful measure for serial follow up in an individual patient, but the absolute volume per se is unlikely to be a reliable guide to severity as it is dependent on haemodynamic variables and chamber size(51). Expressing the regurgitant volume as a ratio of total mitral inflow volume is a more standardised measure(51).

1.3.1.5 Challenges for the quantitative assessment of secondary MR

Secondary MR can be much more challenging to grade than primary MR. The total LV forward stroke volume may be reduced and thus RVol is usually lower

than in primary MR (<60 mL for severe MR if total stroke volume is reduced). Although RF would account for comparative lower flows, its derivation has higher errors due to the small numbers involved(63,64). The regurgitant orifice is also frequently semilunar or elliptical, affecting measurements of VC width and possibly leading to underestimation of EROA by the 2D-PISA method. Additionally, EROA may vary with LV size and LV ejection fraction(65). Thus, in the setting of secondary MR, whilst EROA ≥0.4 cm^2 still denotes severe MR, a lower cut-off of EROA ≥0.2 cm^2 may still be likely severe MR due to the above considerations(65). Adding to the challenges, adjunctive findings are also less helpful because they are often rendered abnormal by the underlying cardiac pathology. For example, most patients with cardiomyopathy have systolic blunting of the pulmonary venous flow pattern due to elevated LA pressure. Another confounding problem is that secondary MR is frequently very dynamic. It is therefore important to consider volume status, blood pressure, and other clinical variables in this context (48).

1.3.1.6 LV ejection fraction and dimensions

LV ejection fraction (LVEF) remains one of the strongest prognostic factors for patients with MR, where mortality is inversely proportional to LVEF(30,31). Estimated LVEF is determined via the Simpsons bi-plane method, whereas LV dimensions are measured using the M-mode method in the parasternal long axis view. An increased LV end-systolic dimension (>40 mm) and an LVEF <60% are indicators of LV systolic dysfunction, poor prognosis, and suggest surgical correction even in the absence of symptoms(29,31). The volume to which the LV contracts at the end of systole is independent on pre-load and is determined by contractility, afterload, and eccentric remodelling. Thus, LV end-systolic dimension and volume are independent factors confounding the use of LVEF in assessing ventricular function(7).

1.3.1.7 Identifying subclinical LV dysfunction

In the context of emptying into a low impedance LA, the LVEF can remain normal for a long period of time whereas LV contractility (i.e. the innate ability of the myocardium to generate force) might already be significantly reduced(66). Some

studies, including a large multicentre study, found that post-operative outcome is improved if patients are operated before LV dysfunction is established (67,68). It is therefore important to identify the early decline of LV contractility, a stage when correction of MR can be undertaken to prevent irreversible myocardial damage. Global longitudinal strain (GLS), LV torsion and systolic tissue Doppler velocities have been these emerging techniques. Several studies (69–72) have also investigated the prognostic value of other non-invasive measures of LV contractility; i.e. end-systolic pressure–volume loop ratio, end-systolic elastance, systolic wall stress versus endocardial shortening, and peak positive dP/dt. Although they are dependent on loading conditions and degree of LV remodelling, some of these indices have been shown to be better than LVEF at identifying patients with MR and preserved LVEF, who have reduced LV contractility(66). The ideal measure of contractility would be a measure independent of pre- and after-load, sensitive to changes in inotropic state, insensitive to LV size, and easy to utilise(7).

Tissue Doppler Echocardiography

Global Longitudinal Strain

LV global longitudinal strain has emerged as a non-invasive strategy to assess LV myocardial deformation and LV contractility in patients with MR(69,73,74). It can be obtained with either Tissue Doppler Imaging (TDI) or bi-dimensional images (2D-speckle tracking). Although strain rates have been demonstrated to correlate well with LV function(75), it has been shown to decrease even before marked increase in LV chamber dimensions (>45mm) occur(76). One study demonstrated that despite similar LVEF, patients with dilated cardiomyopathy and severe functional MR showed more impaired LV global longitudinal strain compared with patients without functional MR (–9.78 ± 3.78% versus –8.08 ± 3.33%; p= 0.004)(73). Witkowski et al.(69) reported that in those with severe asymptomatic MR and preserved LVEF, a GLS below -19.9% could predict post-operative LV dysfunction with a sensitivity and specificity of 90% and 79%, respectively. Similarly, other studies (77,78) have also shown that GLS below -18.1%, measured by speckle tracking echocardiography, is associated with post-operative LV dysfunction (LVEF of <50%) in patients with normal pre-operative LVEF. GLS was also found to be significantly reduced in patients with

asymptomatic significant organic MR and preserved LVEF, which correlated with a significant increase in the myocardial extracellular volume (measure of reactive fibrosis) when using T1 mapping CMR techniques(79). Presumably, the volume overloaded LV leads to an increased interstitial fibrosis and loss of myocytes, hence resulting in the reduction of GLS. The use of GLS assessment could therefore potentially aid in the risk stratification of asymptomatic patients with severe MR. GLS obtained by 2D-speckle tracking method, instead of TDI, is not angle dependent and therefore deemed to be more reliable(80). Nevertheless, some limitations of strain imaging include its dependence on pre-load and afterload. In order to correct for the influence of preload on strain, Marciniak et al. (76) devised a geometry-compensated deformation indices, which can be calculated by dividing strain and strain rate by end-diastolic volume (EDV).

LV torsion

Another application of speckle tracking is the relative easy acquisition of torsional parameters, i.e. twist and torsion (=twist/LV long-axis dimension) (11). Some studies have demonstrated the progressive deterioration of the torsion profile in primary MR, making these parameters promising indicators of subclinical LV dysfunction(81,82).

Systolic Tissue Doppler Velocities

Reduced systolic tissue Doppler velocity at the mitral lateral annulus have also been shown to identify subclinical LV dysfunction and to predict post-operative LV dysfunction in patients with asymptomatic MR(83).

LV ejection index

In 2015, Magne et al (84) studied a novel Doppler-based technique in primary MR: LV ejection index (LVEI). Pre-operative LVEI of >1.13 is found to be an independent predictor of postoperative LV dysfunction (LVEF ≤ 50%) and all-cause mortality, even in patients with a preserved pre-operative LVEF. LVEI index may therefore also be used as a complementary parameter to risk stratify and guide decision making in patients with primary MR(84).

1.3.1.8 Exercise echocardiography

MR is load dependent and its severity can have a dynamic nature which may increase with exercise(85). Exercise/stress echocardiography such as supine-bike exercise, can be used to examine the changes in MR severity and PAP with activity, especially in asymptomatic patients(86–88). The 2016 European Association of Cardiovascular Imaging (EACVI) and American Society of Echocardiography (ASE) guidelines recommend consideration of exercise stress echocardiography when symptoms are disproportionate to the severity of MR at rest (85). The increase in MR severity (≥1 grade), dynamic pulmonary hypertension (systolic PAP ≥60mmHg) and limited right ventricular (RV) contractile recruitment (TAPSE<19mm) are all markers of poor prognosis(85,87). On the other hand, the AHA/ACC guidelines(30) recommend exercise/stress echocardiography in those with asymptomatic severe MR in order to identify high-risk individuals who may benefit from early elective surgery (Class IIa Level C). An increase in in EROA (≥13mm^2) or systolic PAP (≥60mmHg) during exercise have been shown to be associated with decreased symptom-free survival(50,89).

The response to exercise echocardiography has also been used to identify subclinical LV systolic dysfunction in patients with asymptomatic MR. The impaired contractile reserve during peak exercise (defined as <5% increment in LV ejection fraction or a <2% increment in GLS) has the potential to predict decrease in LVEF and worsening of symptoms at follow-up in medically managed patients(85,87). Furthermore, reduced contractile reserve also helps to identify post-operative LV systolic dysfunction and early cardiac events in surgically treated patients(90,91). In one study of 115 asymptomatic patients with moderate-to-severe organic MR, the impaired GLS during peak exercise was associated with an increase in cardiovascular death, MV surgery, and hospitalisation for heart failure (HR 1.6, 95% CI 1.1–2.3, p= 0.01)(71). Exercise imaging may therefore be a practical tool for guiding the optimal timing of intervention, especially in patients in whom the risk to benefit ratio of surgery is uncertain (doubts about reparability, comorbidity, advanced age).

In the setting of secondary MR, stress echocardiography may provide helpful information in the following patients: a) those with dyspnoea on exertion disproportionate to LV systolic dysfunction or MR severity at rest b) those with recurrent and unexplained acute pulmonary oedema c) those with intermediate MR severity and is scheduled for coronary artery bypass grafting (to identify those who may benefit from combined revascularisation and MV repair) and d) those requiring individual risk stratification(85). Unless suspicious of ischaemic MR, there is currently no role for pharmacologic stress echocardiography (i.e. dobutamine) to evaluate severity of MR as its effects on MR severity are not considered physiological(85).

1.3.2 Transoesophageal echocardiography

In severe asymptomatic MR, optimal outcomes are achieved in centres where MV repair rates are high (>95%) and mortality is low (<1%)(29). Assessing the feasibility of successful surgical repair is therefore crucial(3). TOE is able to provide useful information concerning the likelihood of MV repair (i.e. localisation of prolapse and chordal rupture) when TTE is of poor quality or when complex, calcified, or endocarditic lesions are suspected(1,3,6). TOE is recommended in the intra-operative setting for further diagnostic refinement (43) and is also an indispensable imaging tool for guiding percutaneous MV procedures (3). Apart from delineating anatomy of lesions and guiding deployment of the device, it also provides information on its hemodynamic dysfunction pre- and post-repair(3,7). 3D-TOE offers considerable value in localising valve prolapse/flail leaflet and in simulating a ‘surgeon’s view’ of the valve, by orientating the image to exhibit the aortic valve at the 11-o’clock position(8). It is however important to note that TOE is semi-invasive and therefore not suited for serial studies(92).

1.3.3 2D versus 3D echocardiography

Although 2D-echocardiography is the imaging modality of choice for the evaluation of MR severity, it can be affected by limited cut-planes and it is operator-dependent(3). Due to its foreshortened views and geometrical assumptions, 2D-echo consistently underestimates LV volumes(11). In contrast, simultaneous multi-plane imaging by 3D-echocardiography permits accurate

localisation of valve lesions(1,3,43). Despite its lower spatial resolution, it is far superior in the assessment of complex MV pathology especially in the intra-operative setting(90,93). When compared with independent reference imaging modalities (i.e. radionuclide ventriculography or CMR), 3D-echo has been shown to be more accurate and reproducible than 2D-echo in the measurements of LV volumes and LVEF (11,94). PISA can also be viewed in its entirety, obviating the need to make hemispherical shape assumptions for surface area computations.

1.3.4 2D versus 3D parameters for MR severity

Several studies have compared the parameters used in the grading of MR severity (Table 1.3). The largest study (n=221), using CMR as a reference standard, demonstrated that 2D-PISA method significantly under estimated RVol compared with the 3D-PISA method (55.3±19.6 versus 67.4±29.1ml) (95). These differences were more pronounced in patients with severe MR, eccentric regurgitant jet, and asymmetrical regurgitant orifice. Matsumura et al(n=54) (96) found that 3D-PISA more accurately quantifies EROA in MV prolapse but interestingly underestimates EROA by 24% in *functional* MR compared with 2D-quantitative Doppler. This underestimation can be explained by the “elongated” geometry of PISA in functional MR instead of the ‘hemispheric’ assumptions used in its calculation(97). This implies that in patients with *functional* MR, the calculation of EROA should be based on the 2D-quantitative Doppler instead of 3D-PISA method. In eccentric jets however, 3D-EROA planimetry was demonstrated to be superior over the 2D-PISA EROA method (98,99). Although TTE has been a mainstay of MR assessment, it has limited reproducibility (57,100) and relies on mathematical assumptions of LV geometry and cavity size, which may not apply in a remodelled ventricle. Biner et al(57) demonstrated that echocardiographic parameters were only modestly reliable and were associated with suboptimal interobserver agreement. The investigators also found that the assessment of MR severity were discordant in approximately 60% of the cases. A more objective, quantification of MR severity can be obtained with CMR imaging.

Table 1.3 Studies assessing the accuracy of various 2D and 3D echocardiographic techniques for the quantitative evaluation of MR

Studies	N	Mechanism of MR (%)	2D echo	3D echo	Reference modality	Main findings
Iwakura et al(101)	106	Organic 79 Functional 21	EROA-quantitative Doppler: 0.01–1.34 cm^2 EROA-PISA: 0.03–0.99 cm^2	EROA-planimetry: 0.03–1.44 cm^2	n/a	2D PISA underestimated the EROA compared with quantitative Doppler analysis and 3D echo
Yosefy et al(102)	50	Organic 40 Functional 60	EROA-quantitative Doppler: 0.48±0.25 cm^2 EROA-PISA: 0.34±0.14 cm^2	EROA-HE: 0.52±0.17cm^2	n/a	2D PISA underestimated the EROA compared with quantitative Doppler analysis and 3D echo
Shanks et al(103)	30	Organic 47 Functional 53	PISA-Rvol: 53.2±35.3 ml	PISA-RVol: 63.2±41.3 ml	RVol-CMR (LVSV-AoSV): 65.1±42.7 ml	2D PISA underestimated mitral RVol by 21.3% compared with CMR, whereas 3D PISA underestimated mitral RVol by 1.2%
Choi et al(95)	221	Organic 53 Functional 47	PISA-RVol: 55.3±19.6 ml	PISA-RVol: 67.4±29.1 ml	RVol-CMR (LVSV-AoSV): 64.3±28.6 ml	2D PISA underestimated mitral RVol more than with 3D PISA particularly in patients with severe MR, presence of asymmetrical orifice shape and eccentric regurgitant jet
Matsumura et al(96)	54	MVP 50 Functional 50	EROA-quantitative Doppler MVP: 0.45±0.15 cm^2	EROA-PISA MVP: 0.49±0.20 cm^2	n/a	3D PISA underestimated the EROA by 24% in patients with functional MR compared with 2D quantitative Doppler, but not in patients with MVP

			Doppler Functional: 0.38±0.10 cm^2	FMR: 0.20±0.12 cm^2		
Marsan et al (94)	64	Functional 100	VCW-EROA: 0.11±0.12 cm^2 VCW-EROA elliptical: 0.14±0.15 cm^2	EROA-planimetry: 0.22±0.14 cm^2	VE-CMR	2D echo significantly underestimated EROA compared with 3D echo. When compared with VE-CMR, 2D echo underestimated the regurgitant volume by –2.9ml (VCW-EROA) and –1.6ml (VCW-EROA elliptical), whereas 3D echo showed a better agreement (–0.08 ml)
Hyodo et al (104)	60	Functional 100 (multiple jets)	VCW-EROA: 0.17± 0.10cm^2	EROA-planimetry: 0.23±0.13 cm^2	EROA-thermodilution	The correlation of 3D EROA and EROA by thermodilution was better than the sum of multiple 2D VCW in the context of multiple jets (r=0.9 vs 0.56, respectively)
Zeng et al(105)	83	Organic 53 Functional 47	PISA-EROA mild: 0.13±0.05 cm^2 moderate: 0.25±0.08 cm^2 severe: 0.57±0.25 cm^2	EROA-planimetry mild: 0.15±0.06 cm^2 moderate: 0.34±0.09 cm^2 severe: 0.66±0.21 cm^2	n/a	3D EROA improves accuracy of MR grading compared with 2D-PISA method
Kahlert et al(106)	57	Organic 63 Functional 37	VCW-EROA 4-chamber: 0.35±0.26 cm^2 2-chamber: 1.35±1.34 cm^2	EROA-planimetry: 0.62±0.45 cm^2	n/a	3D EROA-planimetry revealed significant asymmetry of the regurgitant orifice in functional MR compared with organic MR, leading to poor estimation of its area by single 2D-VCW measurements

			VCW-EROA elliptical: 0.63±0.45 cm^2 EROA-PISA HS:0.42±0.30 cm^2 HE: 0.53 ± 0.36 cm^2			
Yosefy et al(107)	45	Organic 42 Functional 58	EROA-quantitative Doppler VCW	EROA-planimetry VCW	n/a	No significant differences in EROA were observed between 2D and 3D echo (0.04±0.06 cm^2). 2D and 3D VCW were more similar for central regurgitant jets than for eccentric regurgitant jets
Matsumura et al(97)	30	Functional 100	EROA-quantitative Doppler: 0.38±0.10 cm2	EROA-HS : 0.20 ± 0.10 cm^2 EROA-HE: 0.28 ± 0.11 cm^2	n/a	3D EROA-hemispheric assumption underestimated the EROA
Skaug et al(108)	27	Organic 59 Functional 41	PISA-Rvol: 22.2ml	Multi-beam HPRF colour Doppler RVol: 35.6ml	RVol-CMR (LVSV-AoSV): 35.1ml	2D-PISA underestimated mitral RVol compared with 3D multi-beam HPRF colour Doppler echo

N; number of patients; MR, mitral regurgitation; 2D, 2-dimensional; 3D, 3-dimensional; EROA, effective regurgitation orifice area; PISA-proximal isovolumetric surface area; HE, hemi-elliptic; RVol, regurgitant volume; CMR, cardiovascular magnetic resonance imaging; LVSV, left ventricular stroke volume; AoSV, aortic stroke volume; MVP, mitral valve prolapse; VCW, vena-contracta width; VE. Velocity-encoded; HS, hemispherical; HPRF, multibeam high-pulse repetition frequency.

1.4 Cardiovascular Magnetic Resonance

CMR imaging is the reference standard non-invasive imaging modality for the assessment of ventricular volumes and ejection fractions, and has the additional capabilities of quantifying flow (allowing accurate assessment of valvular regurgitation)(109,110). Over the last decade, CMR has been shown to be a robust method of determining the severity of MR, especially in the absence of other valvular lesions(111–113). It is also able to reliably determine MR RVol irrespective of MR jet geometry and has generally a high inter-observer and inter-study reproducibility, making it ideal for serial assessment (48,114,115). In the case of ischaemic MR, CMR can assess for ischaemia, regional wall motion abnormalities and myocardial viability (116–119). Some studies also suggest that focal fibrosis may be used as an early marker of LV systolic dysfunction(120). Recent work by Myerson et al suggests that quantitative CMR measures of RVol/RF may better predict the need for future surgery than echocardiography (121).

CMR has a number of unique advantages: it provides a view of the entire heart without limitations of body habitus or imaging windows, allows free choice of imaging planes, is free of ionizing radiation and does not require contrast administration(48). CMR should therefore be considered in patients with suboptimal echocardiographic imaging or when there is a degree of uncertainty in the severity of MR, usually in the case of eccentric jets that can be underestimated by echocardiography (92,122).

The limitations of CMR include its inability to be performed in patients with certain implanted devices(123). Since most CMR acquisitions are acquired over multiple cardiac cycles, arrhythmias such as atrial fibrillation or premature ventricular contractions may pose a challenge for standard breath-held phase-contrast velocity encoded CMR sequences(48). CMR is also not as readily available as echocardiography, cannot be performed at the bedside or in some patients with claustrophobia, and is generally a more expensive modality. One other limitation includes the inability to assess pressures inside a vessel or cardiac chamber.

Although CMR can be a good alternative to CT prior to MV surgery (or transcatheter MV repair/replacement), it does not show the degree of calcification well and its spatial resolution does not permit robust assessment of coronary artery anatomy (92).

1.4.1 Assessing mechanisms of MR with CMR

Like echocardiography, CMR can identify morphologic abnormalities of the MV apparatus. The presence of billowing, prolapse or flail segments can be identified by dedicated cine imaging performed through the different scallops of the MV leaflets(124). In secondary MR, CMR offers accurate assessment of LV dilation and function in addition to identification of myocardial and papillary muscle scar (125). Mitral valve anatomy can be imaged by acquisition of standard short-axis, two-, three-, and four-chamber long-axis views in combination with oblique long-axis cines orthogonal to the line of coaptation (126).

Due to lower spatial and temporal resolution, imaging of the mitral sub-valvular apparatus (i.e. flail leaflet) with CMR is suboptimal (127). It is also not ideal for detecting vegetations which can be small and highly mobile. CMR however has been shown to have good agreement with TOE with regard to valve leaflet characterisation and has the ability to cross-cut the valve in any plane in order to characterise the aetiology of the MR(124,127). Although visualisation of MV structure and motion is more reliable by echocardiography, CMR is more accurate than echocardiography in quantifying the severity of MR(111,128), as recently demonstrated in a prospective multicentre trial(129).

1.4.2 Assessing severity of MR with CMR

MR can be assessed with CMR by qualitative, semi-quantitative or quantitative methods. As a crude guide to severity, the extent of signal loss due to spin dephasing can be visually observed in the LA on cine CMR acquisitions(130–133) (Figure 1.4).

Alternatively, planimetry of the anatomical regurgitant orifice area (AROA) from the cine CMR acquisitions of the valve can be performed(130,134). AROA planimetry is however time consuming and remains challenging because of appropriate plane alignment and angulation. Quantitation of MR severity (i.e. RVol) is the most robust method of CMR assessment of regurgitation and can be derived using the 3 different CMR techniques (direct/indirect) described below(113,135,136). Direct assessment of flow in the MV (Method 1-Phase contrast technique) is often less accurate due to the significant motion of the MV plane during systole (137). For this reason, quantification of RVol is more commonly performed using the indirect approach, either by comparing ventricular stroke volume to aortic forward flow (Method 2) or comparing LV and RV stroke volumes (Method 3) (48).

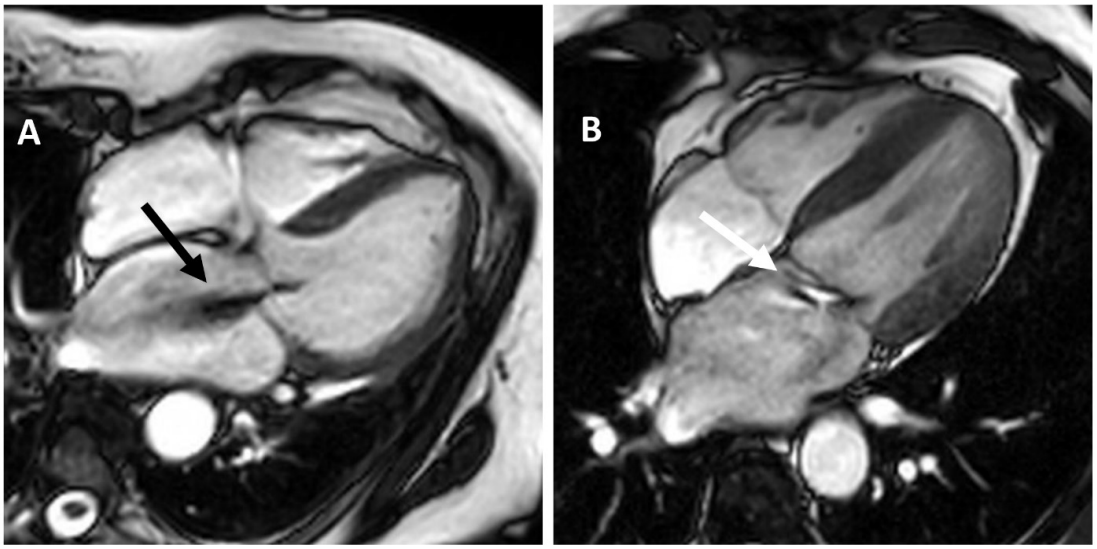

Figure 1.4 Cardiovascular magnetic resonance in mitral regurgitation

(A) Four-chamber cine image showing MV prolapse and a central jet of MR (black arrow) (B) The white arrow (eccentric jet of MR) points to a central bright jet core, with a dark streak of signal loss beyond.

1.4.3 Quantitative assessment of MR severity

Method 1: Phase contrast imaging of the MV

Phase-contrast velocity-encoded mapping is traditionally used to measure blood flow (138). A velocity image, also known as phase map, is generated in which pixel signal intensity and grey-scale colour depends upon the velocity and direction of blood flow (different phase value)(138). Although this method of quantifying flow is considered the reference standard technique, it is however reliant on the ability to transect the jet at 90° in a single direction, and therefore can underestimate flow if this is not achieved(128,139). Direct measurement of the MR jet can be performed with this method by aligning the plane to the MR jet, but this can be challenging due to jet eccentricity, multiple jets and jet turbulence(140). 3D-cine (time-resolved) phase-contrast CMR with three-directional velocity-encoding ('4D flow CMR') is now an emerging technique allowing quantification of flow within the entire heart in all directions, allowing comprehensive flow data to be obtained(141).

Method 2: Difference between LV stroke volume and aortic forward flow volume

Equation 4 CMR quantitation of MR- indirect method (LVSV-Ao flow)

$$RVol = \text{LV}_{\text{SV}} - \text{Aortic}_{\text{forward flow}} = [LV_{EDV} - LV_{ESV}] - [Flow\ SV_{aortic}]$$

$$RF = \frac{\text{RVol}}{LV_{sv}}\ x\ 100\%$$

RVol is derived by calculating LV stroke volume from the short axis cine stack [End diastolic volume (EDV) – end systolic volume(ESV)] and deducting the aortic forward flow derived from the aortic phase contrast velocity-encoded cine images(113,136)(Figure 1.5). This method is highly reproducible and considered robust as it is not affected by the direction or eccentricity of the regurgitant jet, is not affected by the presence of aortic regurgitation and makes no hemodynamic or LV geometry assumptions, as is often the case in echocardiography(115,129,142). This CMR (volumetric) method was also recently found to have the highest diagnostic value to detect significant MR with an area under the curve (AUC) of 0.98, followed by 3D-echo (AUC = 0.96), 2D-echo (AUC = 0.90), and CMR (phase contrast; AUC = 0.83)(143).

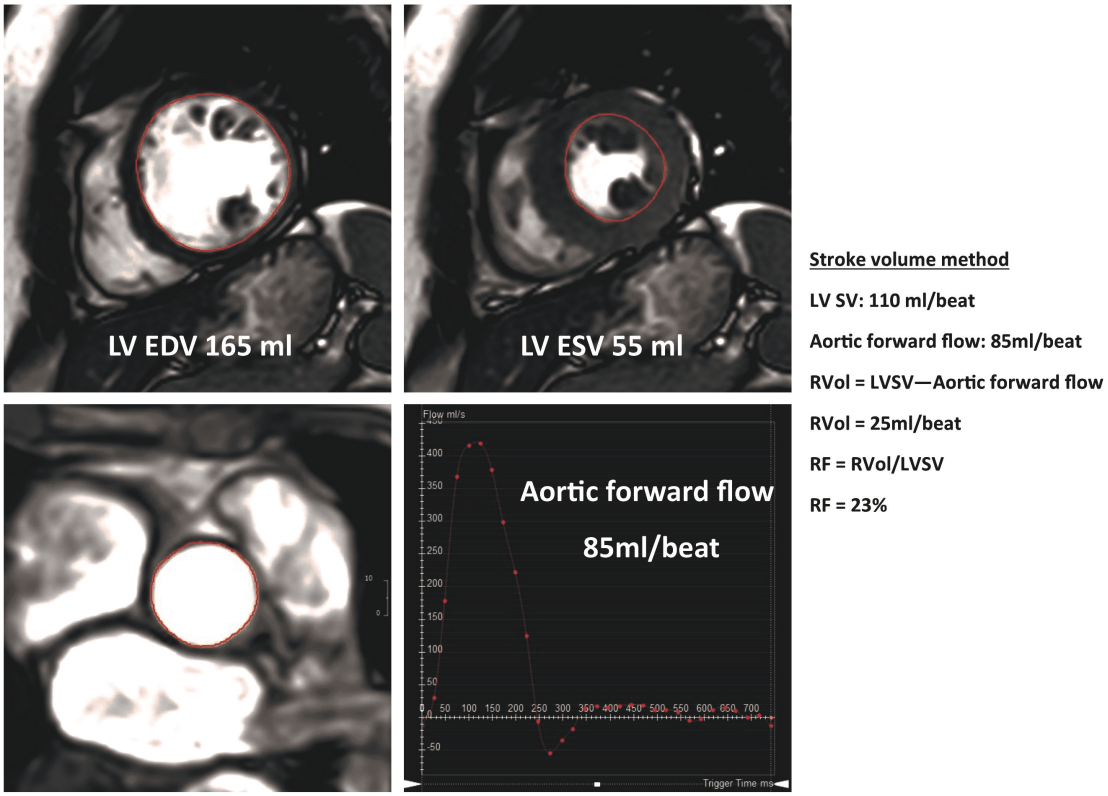

Figure 1.5 Calculation of regurgitation volume by subtracting aortic forward flow from left ventricular stroke volume (LV SV)

LV endocardial contours are traced in systole and diastole from a short-axis stack from base to apex. Aortic forward flow is measured using through-plane phase-contrast MRI. Rvol, mitral regurgitation volume; RF, regurgitation fraction

Method 3: Difference between LV stroke volume and RV stroke volume

Equation 5 CMR quantitation of MR- indirect method (LVSV-RVSV)

$$RVol = LV_{SV} - RV_{SV} = [LV_{EDV} - LV_{ESV}] - [RV_{EDV} - RV_{ESV}]$$

$$RF = \frac{\text{RVol}}{LV_{sv}} \; x \; 100\%$$

This technique is more prone to error and fails in the context of multiple valvular lesions(113). The calculation of the right ventricle stroke volume is also less reproducible due to the extensive trabeculation of the right ventricle.

1.4.4 Grading of MR severity

Reference ranges for MR quantification are yet to be as firmly established as those for echocardiography, however, reference ranges for values acquired via quantitative techniques are outlined in Table 1.4 (111). Myerson et al found that progression to symptoms and need for MV surgery were seen with a RF of >40%(121). Whilst echocardiography remains the first-line modality for assessment of valvular regurgitation, CMR is increasingly used due to its ability to provide absolute quantitation of both mitral RVol and RF.

Table 1.4 Grading of MR severity by CMR thresholds (111)

Severity Grade		Regurgitation fraction by CMR
0	Trivial	<5%
1+	Mild	5 - 15%
2+	Moderate	16 – 25%
3+	Moderate-severe	26 – 48%
4+	Severe	>48%

1.4.5 Concordance between echo and CMR

There are a paucity of comparative studies between echocardiography and CMR, and the majority have shown a modest concordance in the qualitative or quantitative evaluation of MR(64,111,114,115,129,144). The latest study demonstrating a modest correlation for RVol/RF parameters has utilised the volumetric PW-Doppler flow quantitation(64). Contrary to above, a prospective multicentre study by Uretsky et al found that compared to CMR, echocardiographic grading of MR severity was higher and 2D-PISA-derived RVols were larger(129). This discordance was particularly marked in patients who were referred for MV surgery based on the current ACC/AHA recommendations. Amongst the patients referred, approximately two-thirds did not have severe MR by CMR. A tight correlation was found between the RVol calculated using CMR and the degree of LV negative remodelling post-MV surgery, suggesting that RVol by CMR is more accurate than PISA-based RVol by echocardiography. Furthermore, there was no relationship between the PISA-derived RVol (echo) and the degree of LV negative remodelling post-surgery.

In 2016, a retrospective analysis of asymptomatic patients with moderate-severe MR by echocardiography followed patients for a mean duration of 2.5±1.9 years for progression to an indication for MV surgery(121). Patients who did not progress to an indication for surgery and those who did both had mean RVol by echocardiography in the severe range (74±74 ml vs 89±36 ml). By CMR, those who did not progress to an indication for MV surgery had lower mean RVol than those who did progress (39±20 ml vs 66±24 ml). In this study, RVol by CMR had an AUC of 0.80 for determining which patients would develop an indication for MV surgery. A cut-off of CMR-derived RVol of 55 ml differentiated those who progressed to an indication for surgery from those who did not. However, a cut-off of an EROA of 0.4cm^2 by echo could not differentiate these two groups. These findings have emphasised the predictive value of CMR quantitative parameters in patients with MR. It is also important to note that although the methods for determining severity of MR by echocardiography differ amongst the studies, the method for CMR has been consistent, highlighting the consensus of a single reproducible method for quantifying MR by CMR. The advantages and limitations of each imaging modality in the assessment of MR are summarised in Table 1.5.

1.4.6 Late gadolinium enhancement

Late gadolinium-enhancement by CMR (LGE-CMR) is an attractive technique to noninvasively detect myocardial fibrosis and infarction (116–119). Indeed, gadolinium-based contrast agents have extravascular distribution volume, which increases when the extracellular matrix proliferates or when myocytes are replaced by focal fibrosis(116). The presence of LGE (i.e infarct/scar) provides insight into the mechanism of functional MR.

One study found that the presence of fibrosis at the level of the papillary muscle in the infero-basal LV wall were associated were associated with complex ventricular arrhythmias in patients with MV prolapse(145). Another found that the presence of late gadolinium enhancement on CMR imaging of patients with moderate or severe primary MR is associated with LV dilatation, suggesting that fibrosis occurs once LV remodelling is heralded(120). Theoretically, fibrosis may

therefore be a prognostic marker of outcome that could alert the clinician to irreversible myocardial damage and could be used as an early marker prior to overt systolic dysfunction. This may be helpful in guiding when to adopt a "surgery now" approach as opposed to a "watchful waiting" approach.

Table 1.5 Pros and Cons of each imaging modality in the assessment of MR(50,51,56,57)

	PROS	CONS
TTE	• Greater portability and availability • Multiple methods to assess MR severity • Assess calcium distribution	• Limited cut planes and is operator-dependent • Acoustic window limitations • Reliant on geometric assumptions • Caveats in assessing eccentric MR jets • Reproducibility
TOE	• Portability and availability • Assess suitability for repair • Visualise intraoperative surgical view • Mathematical model provides specific measurements essential for surgeons	• Semi-invasive, not suited for serial studies • Reliant on geometric assumptions
3D echo	• Comprehensive and dynamic view of MV anatomy • Ability to reformat data as desired • Good for volumes	• Stitching artefact • Low temporal resolution with single heartbeat data • Time-consuming reconstructions
Exercise echo	• Assess changes in MR, LV function and PAP with exercise	• Deconditioned patients with limited exercise capacity • Challenging image acquisition
CMR	• No body habitus/ acoustic window limitations • Free choice of imaging planes	• Not widely available • Contraindications (i.e. some pacemakers, defibrillators)

	• Accurate/reproducible • Excellent CNR and SNR • LV volume measurements without geometric assumptions • Severity based on quantitation of RVol/RF • Not affected by jet direction or presence of multiple jets • Ability to assess myocardial viability and scarring	• Longer scan • Compromised quality in the setting of arrhythmias • Lower temporal resolution; hence not ideal for detecting small vegetations and possible underestimation of flow • Limited data on Rvol and RF cut-offs for severity grading and limited outcome data available based on the grading
CARDIAC CT	• No body habitus/ acoustic window limitations • Highest spatial resolution, CNR & SNR • Accurate measurement of MV geometry and leaflet lengths and angles • Assess extent of calcification of the mitral annulus	• Radiation exposure (high dose if data acquired throughout the cardiac cycle for functional assessment) • Nephrotoxic contrast • Not suitable for arrhythmia due to ECG-gated acquisition • Poor temporal resolution • Inability to assess flow

PAP, pulmonary arterial pressure; CNR, contrast noise ratio; SNR, signal-noise-ratio; RVol, regurgitant volume; RF regurgitant fraction

1.5 Cardiac CT

Multi-slice Cardiac CT can be particularly useful in the pre-operative setting as it provides complementary information on the feasibility and safety of MV repair or replacement. In addition to evaluating the extent of MV annulus calcification(146), cardiac CT can provide detailed measurements of the MV geometry and assess the angle in between the anterior MV and LVOT tract to aid pre-procedural planning; thus reducing the risk of LVOT obstruction during newer transcatheter techniques of MV replacements (103,146,147). The use of cardiac CT also allows the simultaneous visualization of the cardiac arterial and venous systems, and cardiac anatomy which can further aid the planning of percutaneous MV repair(7). Although cardiac CT with cine imaging can reliably detect and localise segmental leaflet prolapse, this is not routinely performed due to the high radiation dose required(148). Similarly, whilst cardiac CT is particularly useful in excluding coronary artery disease (high negative predictive value in patients who are at low risk of atherosclerosis), its routine use for this in the setting of valvular heart disease is not yet recommended.

In terms of assessing MR severity by cardiac CT, two studies have demonstrated that CT-derived AROA correlates well with EROA measured by echocardiography(148,149). Quantitative RVol can be generated as the difference between the calculated stroke volume of the left and the right ventricle and has been shown to have a good correlation with the RVol obtained by CMR (150). An important caveat is that this technique is not be feasible in the presence of other valve dysfunction. Cardiac CT could however be an alternative for patients with poor echo imaging when CMR is contra-indicated. Whilst routine assessment with cardiac CT is not yet recommended, its role might increase as radiation and contrast doses decrease in the future.

1.6 SUMMARY

As each imaging modality has its intrinsic advantages and limitations, an integrated multimodality imaging approach is essential for a comprehensive assessment of MR. Although echocardiography is widely accessible and offers excellent morphological and functional information, it is limited by its suboptimal reproducibility in severity assessment and in its evaluation of secondary MR. CMR is highly accurate in the quantitation of MR severity and should be considered in those with eccentric MR or poor echocardiographic images. The data surrounding the use of CMR in the assessment of degenerative MR, which often has an eccentric jet, is currently sparse. More research in this field is needed to inform future clinical guidelines and protocols.

1.7 Thesis aims and hypotheses

Mitral regurgitation is the second most frequent valve disease in Europe after aortic valve stenosis and results in significant morbidity and mortality(2,151). This thesis will focus on studying degenerative MR as it is the most common aetiology of mitral incompetence, and timely surgical correction can lead to improved outcomes(3,152). In addition, it is a relatively more homogenous group of patients when compared to those with ischaemic MR, leading to fewer confounding factors such as the degree of ischaemia or regional wall abnormalities during analysis of data. Furthermore, as described earlier, the prolapse of MV leaflets in degenerative MR often results in an eccentrically directed jet of MR where MR assessment with echocardiographic parameters can be less reliable. Accurate assessment of MR severity and its associated complications are important, as it not only determines timing and indication for surgical correction, but also carries significant prognostic implications. Whilst advanced echocardiographic techniques are superior in the evaluation of complex MV anatomy, CMR appears the most accurate technique for the quantification of MR severity and for its volumetric assessment(114,129,140). CMR imaging is therefore ideally placed to comprehensively assess MR in various clinical settings. With CMR being the investigative tool, the aims/hypotheses of the thesis are outlined for each chapter:

Chapter 3) To assess the impact of MR severity on cardiac reverse remodeling and patients' outcome in the transcatheter aortic valve implantation (TAVI) population. *Hypothesis:* In the TAVI population, improvement in MR severity is associated with a higher degree of positive LV reverse remodeling.

Chapter 4) To assess the impact of MV repair versus MV replacement on cardiac reverse remodelling, comparing it to a group of patients under watchful waiting. *Hypothesis:* In the new era of MV replacement with chordal preservation, there would be no difference between MV repair and replacement strategies in the degree of cardiac reverse remodelling.

Chapter 5) To evaluate the feasibility and reproducibility of a free-breathing, multi-shot, navigated cine image acquisition method for biventricular physiological assessment during continuous physical exercise in healthy volunteers. *Hypothesis:* Exercise CMR protocol using the free-breathing, multi-shot, navigated cine image acquisition for ventricular assessment during continuous physical exercise is feasible and has a good intra- and inter-observer reproducibility.

Chapter 6) To evaluate the feasibility of navigated exercise CMR in patients with significant MR and quantify their exercise-induced changes in ventricular volumes and MR severity. *Hypothesis:* The navigated exCMR protocol is feasible in patients with significant valvular heart disease, and MR severity worsens with exercise.

Each topic has been studied and discussed in depth and forms a results chapter in its own right, with an appropriate introduction, methods, results and discussion section. Chapter 2 will outline the general methodology adopted in this thesis. As some methodologies are unique to each individual study, they are described within the methods section in their respective chapters.

Chapter 2 METHODS

As each results chapter has its own unique set of patient population, CMR scan protocol and parameters, and specific inclusion/exclusion criteria, this chapter will outline the common methodologies used in this thesis.

2.1 Patient selection and recruitment

Participants in this thesis work were recruited from a single tertiary centre, Leeds Teaching Hospitals NHS Trust, Leeds, UK. General exclusion criteria included: any contraindications to CMR, renal failure with an estimated glomerular filtration rate of <30ml/min/1.73m^2, weight >130kg, uncontrolled AF >120bpm, pregnancy or breast feeding, haemodynamic instability, New York Heart Association (NYHA) functional Class IV, or inability to lie flat for 60 minutes. Significant MR on echocardiography was defined according to the ASE guidelines (11), which involves a combination of both qualitative and quantitative measurements: vena contracta >0.7cm^2, PISA radius >0.8cm, MR volume >45ml/beat, MR fraction >40%, EROA >0.3cm^2. All patients provided written informed consent.

2.2 CMR protocol

Scans were performed on a 1.5T MRI system (Intera, Phillips Healthcare, Best, Netherlands) equipped with a 70cm bore.

2.3 CMR analysis

CMR analysis was performed using dedicated computer software (CVI^{42}, Circle Cardiovascular Imaging, Calgary, Alberta, Canada). LV endocardial and epicardial borders were manually contoured (with trabeculation and papillary muscles excluded) at end-diastole and end-systole to allow the calculation of ventricular volumes (summation of discs methodology) (153) and LV mass (epicardial volume – endocardial volume multiplied by myocardial density (1.05g/cm^3)); values were indexed to body surface area (Mostellar formula).

Stroke volume was measured as the difference between end-diastolic and end-systolic volume, whereas cardiac output was calculated as: SV x HR. Left atrial volume was calculated using the formula:

$$\frac{8(A2_{Ch})(A4_{Ch})}{3\pi L}$$

where $A2_{Ch}$ and $A4_{Ch}$ refer to the left atrial area in the two-chamber and four-chamber views respectively, and L is the shorter of the two left atrial length measurements.

Phase contrast velocity mapping in the aorta was obtained at the sino-tubular junction. Contouring of the aortic lumen was performed to provide forward flow volume through the aortic valve. In those with AF, flow measurement from 2 acquisitions were averaged. The regurgitant volume through the mitral valve (i.e. MR volume) was calculated using the indirect flow method (154) using the below equation:

$$\textit{MR volume} = LV_{SV} - \text{Aortic}_{\text{forward flow}} = [LV_{EDV} - LV_{ESV}\,] - [Flow\ SV_{aortic}]$$

MR fraction (%) was then quantified using the following equation:

$$\textit{MR fraction} = \frac{\text{MR Volume}}{LV_{sv}}\ x\ 100\%$$

As CMR imaging modality was used to quantitate the degree of MR severity in this study, it is felt that the degree of MR is best classified according to CMR classifications by Gelfand et al(111) where MR is classified based on its MR fraction: mild ≤15%, moderate 16–25%, moderate-severe 26–48%, severe >48%.

2.4 Statistical analysis

All statistical analysis was performed using the SPSS V.22.0 (IBM Corp., New York, USA). All continuous data were tested for normality using the Shapiro-Wilk test; variables were expressed as mean±SD or median (IQR) in cases of skewed

distributions. Categorical variables are expressed as frequencies and percentages. For normally distributed continuous data, two-tailed unpaired Student's *t* tests were used for comparisons between groups, and paired Students *t* tests were used for intra-group comparisons. For non-normally distributed data, Mann-Whitney U-test was used. The Chi-squared test was used for comparing categorical variables. When assessing correlation between dependent and independent variables, Pearson's correlation coefficients were used. Two-sided P values <0.05 were considered statistically significant. Univariate analysis was used to determine predictive factors. Variables with a univariate $p<0.1$ were entered into multi-variable regression analysis. Cumulative survival was analysed with Kaplan-Meier methodology and log-rank test.

Chapter 3 CMR quantitation of change in Mitral Regurgitation following Transcatheter Aortic Valve Implantation (TAVI): Impact on left ventricular reverse remodelling and outcome

3.1 ABSTRACT

Background

Current echocardiographic data reporting the impact of concomitant mitral regurgitation (MR) on outcome in patients who undergo transcatheter aortic valve implantation (TAVI) are conflicting. Using CMR imaging, this study aimed to assess the impact of MR severity on cardiac reverse remodelling and patient outcome.

Methods

85 patients undergoing TAVI with CMR pre- and 6m post-TAVR were evaluated. The CMR protocol included cines for LV and RV volumes, flow assessment, and myocardial scar assessment by late gadolinium enhancement (LGE). Patients were dichotomised according to CMR severity of MR fraction at baseline ('non-significant' versus 'significant') and followed up for a median duration of 3 years.

Results

Forty-two (49%) patients had 'significant MR' at baseline; they had similar LV and RV size and function compared to the 'non-significant MR' group but had greater LV mass at baseline. In those with significant MR at baseline, 77% (n=32) had a reduction in MR post-TAVI, moving them into the 'non-significant' category at 6-months, with an overall reduction in MR fraction from 34% to 17% ($p<0.001$). Improvement in MR was not associated with more favourable cardiac reverse remodelling when compared with the 'non-improvers'. Significant MR at baseline was not associated with increased mortality at follow-up.

Conclusions

Significant MR is common in patients undergoing TAVI and improves in the majority post-procedure. Improvement in MR was not associated with more favourable LV reverse remodelling and baseline MR severity was not associated with mortality.

3.2 INTRODUCTION

Transcatheter aortic valve implantation (TAVI) has been shown to reduce mortality and improve patient symptoms and quality of life (155–157), and is an alternative to surgery in intermediate and high-risk patients with severe aortic stenosis (AS) (158). Whilst moderate or severe MR is seen in up to 48% of patients undergoing TAVI, it is often left untreated (159–161). Current literature reporting the impact of concomitant MR on outcome in patients who undergo TAVI are conflicting and are mainly based on echocardiographic data; which can be limited by poor acoustic windows, eccentric jets and geometric assumptions (140). CMR imaging is able to quantify MR with high accuracy and reproducibility using a combination of LV volumetric measurements and aortic flow quantification (112,114,121). Tissue characterization is a further unique strength of CMR, offering non-invasive detection of myocardial fibrosis (162). In a TAVI population however, quantitative serial assessment of MR by CMR has never been specifically studied, despite its objectiveness, reproducibility and accuracy.

The aims of this study were to 1) to quantitate the change in MR severity at 6-months post-TAVI using CMR, 2) identify predictors of MR improvement and its association with LV reverse remodelling, 3) assess the clinical impact of MR on the outcomes of patients undergoing TAVI.

Hypothesis: In the TAVI population, improvement in MR severity is associated with a higher degree of positive LV reverse remodeling.

3.3 METHODS

3.3.1 Study design and population

In this post hoc analysis of a prospective study, 109 patients with severe AS undergoing TAVI between April 2009 and September 2015 at a single tertiary centre (Leeds General Infirmary, Leeds, UK) were evaluated. The flow diagram in Figure 2.1 demonstrates the patient recruitment pathway with reasons for non-

completion of study protocol. Severe AS was defined as an echocardiographically derived aortic valve area of ≤1.0cm^2, peak aortic velocity of >4m/sec or mean pressure gradient of >40mmHg. Decision for TAVI intervention was taken by a multidisciplinary heart team in accordance with international guidance (Logistic EuroSCORE >20 or inoperable co-morbidities). Exclusion criteria included any contraindications to CMR. Baseline clinical, demographic and echocardiographic data were recorded for all patients. CMR scans were performed at baseline and 6-months post-TAVI.

All patients were followed up for a median duration of 3 years and their long-term outcomes were evaluated. Mortality data were obtained from the Office of National Statistics, UK. All patients provided written informed consent. The study was approved by the National Research Ethics Service (08/H1307/106) and complied with the Declaration of Helsinki (See Appendix).

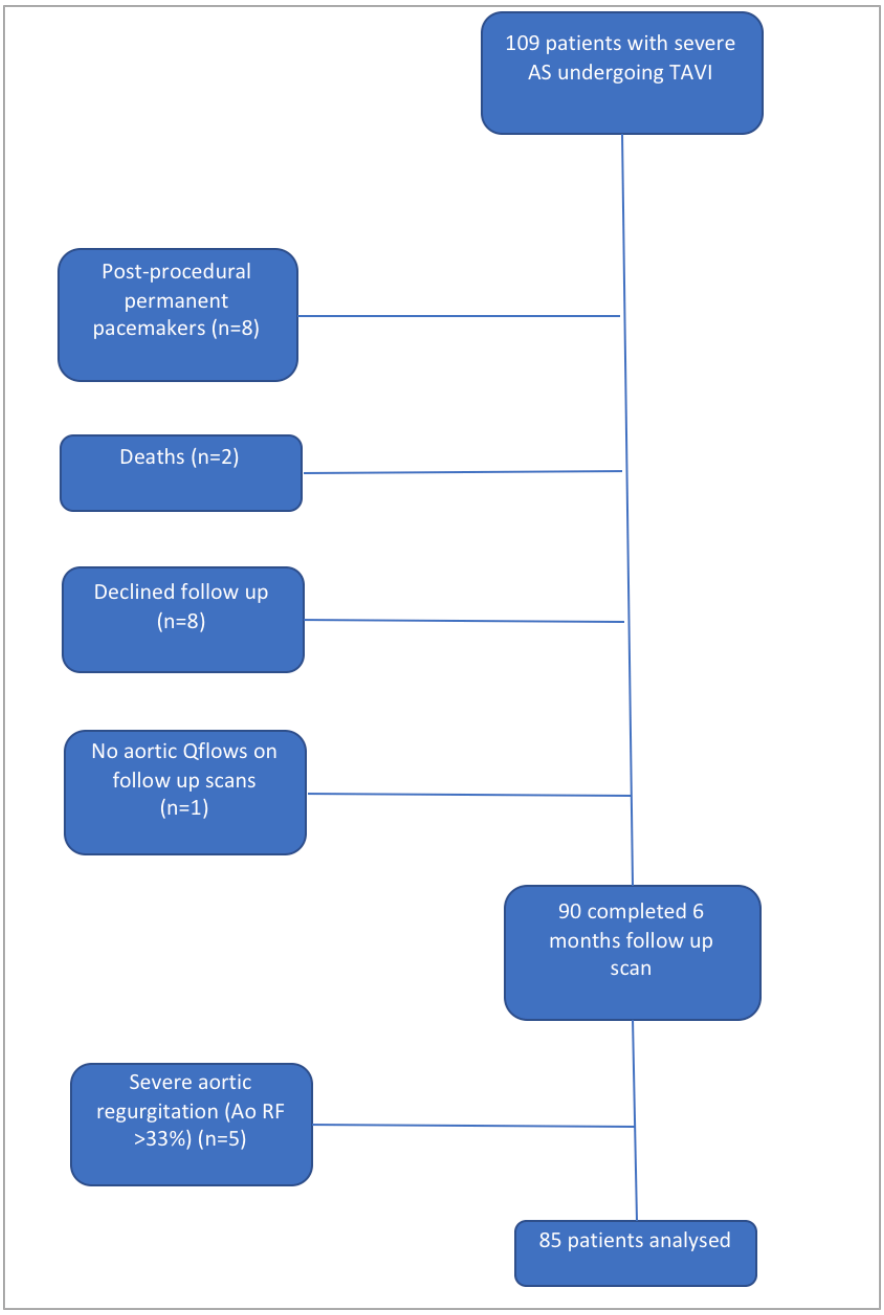

Figure 3.1 Patient recruitment pathway

AS, aortic stenosis; TAVI, transcatheter aortic valve implantation

3.3.2 TAVI

Patients underwent a standard work-up for TAVI which included transoesophageal echocardiography and invasive coronary angiography, with the addition of cardiac computed tomography after 2014. Coronary revascularisation was only performed in those with critical proximal lesions or

symptomatic angina. TAVI was performed under general or local anaesthetic using the self-expanding Medtronic CoreValve (Medtronic Inc, Minneapolis, MIN) or the mechanically expanded Boston Lotus valve (Boston Scientific Corporation, Natick, MA) by two experienced, high-volume operators performing over 150 implants/year. The percutaneous femoral route was the preferred choice if vascular access was suitable. In the presence of significant peripheral vascular disease, alternative routes such as subclavian, carotid, direct aortic or apical were utilised. All patients received heparin to maintain an activated clotting time >250 seconds and were treated with dual antiplatelet therapy (aspirin and clopidogrel) for 3 to 6 months after the procedure.

3.3.3 CMR protocol

Identical baseline preoperative and 6-month postoperative scans were performed on a 1.5T MRI system (Intera, Phillips Healthcare, Best, Netherlands or Avanto, Siemens Medical Systems, Erlangen, Germany); same scanner vendor used at baseline and 6-months. Multi-slice, multi-phase cine imaging was performed using a standard steady-state free precession pulse sequence in the short axis (repetition time (TR) 3msec, echo time (TE) 1.7msec, flip angle 60^0, SENSE factor 2, 8mm thickness, 0mm gap, 30 phases, matrix 192x192, typical field of view (FOV) 340mm) to cover the entire left and right ventricle. Through-plane velocity encoded (VENC) phase contrast imaging was performed at the aortic sino-tubular junction (VENC 250–500cm/s, retrospective gating, slice thickness 6mm, 40 phases, FOV 340mm) or just above the valve prosthesis post-implantation. VENC was typically set at 400-500cm/sec on the baseline scan and 250cm/sec post-procedure. If aliasing occurred at the pre-set VENC, sequential phase contrast imaging was performed at increasing VENC settings until the aliasing artefact had disappeared.

LGE imaging (10–12 short axis slices, 10mm thickness, matrix 240×240, typical FOV 340mm) was performed following a Look-Locker sequence (inversion time scout), 10min after the administration of 0.2mmol/kg of gadoteric acid (Dotarem, Guerbet, Villepinte). Four chamber, two chamber and LVOT views were also

obtained as standard. Cross-cuts and phase swaps imaging were used where necessary for further clarification of the presence/absence of LGE.

3.3.4 CMR analysis

CMR analysis was performed by two experienced CMR operators (PGC, LED) blinded to clinical details. Ventricular volumes, LV mass, left atrial volume and MR fraction (%) were calculated based on the general methodology described in Chapter 2. 'Significant MR' was defined as MR fraction >25% and 'non-significant MR' was defined as MR fraction ≤25% (111). For the purpose of this study, 'significant MR' represented moderate-severe/severe categories and 'non-significant MR' comprised categories of trivial/mild/moderate as per CMR classification. Changes in the MR severity were assessed between the baseline and 6-month post-procedure scans. Those with a reduction in MR severity grade from 'significant' to 'nonsignificant' category were classified as 'improvers', and those without (i.e. MR worsened or unchanged) were labelled as 'non-improvers'.

LGE images were reviewed for the presence or absence of hyper-enhancement, which was then classified as either non-infarct pattern (myocardial fibrosis), infarct pattern, or mixed pattern. Presence of new LGE was determined by direct comparison of pre- and post-procedure scans. In those slices deemed to have LGE present, epi and endocardial contours were manually drawn, with care taken to exclude blood pool, artefacts, fat and pericardial lining. The number and location of segments containing LGE were classified according to the AHA 17-segment model. Myocardial fibrosis was defined as a region of LGE with signal enhancement >5 SD of the signal intensity of non-enhanced myocardium(163).

3.3.5 Statistical analysis

General statistical methods were as described in Chapter 2. Univariate analysis was used to determine predictive factors for MR improvement. Variables with a univariate $p<0.1$ were entered into multi-variable regression analysis.

3.4 RESULTS

3.4.1 Patients and baseline characteristics

From 109 patients with a baseline scan, those with a permanent pacemaker (n=8), severe aortic regurgitation (n=5) or who had an incomplete scan (n=1), were excluded from analysis. Eight patients declined follow-up and 2 patients died prior to their 6-month scan. 85 patients with paired CMR scans (55% male gender, mean age 80±7years) who underwent TAVI for severe AS were included in the final data analysis. Basic demographics and clinical data can be seen in Table 2.1.

In total, 42/85 (49%) patients were classified as having ‘significant MR’, and 43/85 (51%) as ‘non-significant MR’. Those with ‘significant’ MR had a mitral regurgitant volume of 34.5±9.9ml and a regurgitant fraction of 34.2±5.5%. Comparatively, those with ‘significant’ MR had a greater echocardiographically measured aortic peak forward flow velocity (4.8±0.47m/s vs 4.6±0.51m/s, p=0.02), although mean pressure gradient and aortic valve area did not differ significantly. The ‘significant MR’ group (n=42) had similar LV and RV cavity size and function but had greater LV mass at baseline compared to the ‘non-significant MR’ group (Table 2.2). Those with significant MR also had more aortic regurgitation (aortic regurgitant fraction 13.3±6.3% vs 9.5±8.4%, p=0.008) by CMR. The presence of LGE was not statistically different between groups (‘significant’ 21.4% (n=9) vs ‘non-significant’ 34.8% (n=15), p=0.188).

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Table 3.1 Baseline demographics in all patients, 'Non-significant' and 'Significant' MR groups

	All patients	Non-significant MR (n=43)	Significant MR (n=42)	p value
Age at TAVI	80.2 ± 4.9	80.1±7.2	80.2±7.5	0.93
Male sex, n (%)	47 (55)	23 (53)	24 (57)	0.73
Logistic Euroscore	19.8±13.1	19.6±13.1	20.0±13.2	0.80
Euroscore II	5.45±4.42	5.4±4.4	5.5±4.4	0.80
STS Mortality	4.8±2.97	5.1±3.3	4.4±2.5	0.20
STS morbidity	23.2±8.42	23.7±8.3	22.7±8.5	0.50
HTN	44.7%	46.5%	42.8%	0.70
DM	20.0%	20.9%	19.0%	0.80
AF	21.2%	25.5%	16.6%	0.30
MI	22.4%	20.9%	23.8%	0.80
CABG	29.4%	20.9%	38.0%	0.08
PCI	25.9%	25.5%	26.1%	0.90
PVD	21.2%	23.2%	19.0%	0.60
CVA	15.3%	13.9%	16.6%	0.70
PHT	37.6%	30.2%	45.2%	0.15
Revascularization pre-TAVI	8 (9)	4 (9)	4 (10)	0.63

Aortic valve parameters (Echocardiogram)				
AVAi (cm^2)	0.33±0.84	0.33±0.09	0.33±0.07	0.99
AV max velocity (m/s)	4.7±0.51	4.6±0.51	4.8±0.47	0.02
AV mean PG (mmHg)	49.7±11.6	47.5±10.8	51.9±12.1	0.07

Data as mean±SD, n (%). AF, atrial fibrillation; AV, aortic valve; AVAi, aortic valve area (indexed); CABG, coronary artery bypass graft; CVA, cerebrovascular attack; DM, diabetes mellitus; HTN, hypertension; MI, myocardial infarction; PCI, percutaneous coronary intervention; PG, pressure gradient; PHT, pulmonary hypertension; PVD, peripheral vascular disease; STS, Society of Thoracic Surgery; TAVI, transcatheter aortic valve implantation

Table 3.2 Baseline CMR characteristics of patients in all patients, 'non-significant' and 'significant' MR groups

	All patients	Non-significant MR (n=43)	Significant MR (n=42)	p value
LV Mass (g)	138.2±35.3	127.5±31	149±32.9	0.007
LV Mass index (g/m^2)	76.1±18.3	73.5±16.5	83.3±23.3	0.01
LVEDV (ml)	179±49.3	170±44.2	183±45.3	0.33
LVESV (ml)	84.2±43.5	86.7±50.8	81.7±34.9	0.59
LVEF (%)	54.8±12.2	52.5±13.3	56.3±11	0.14
RVEDV (ml)	139.9±36.0	135.6±32.1	144.3±39.5	0.27
RVEF (%)	54.2±9.5	53.5±10.7	55.0±8.8	0.46
LA volume (ml)	131.8±45.0	130.9±51.4	132.8±38.1	0.85
LA volume index (ml/m^2)	72.8±24.9	73.0±28.8	72.6±20.7	0.94
MR volume (ml)	22.4±15.0	10.3±8.1	34.5±9.9	<0.001
MR fraction (%)	22.6±13.3	11.4±9.0	34.2± 5.5	<0.001
Aortic regurgitation fraction (%)	10.9± 7.5	9.5± 8.4	13.3± 6.3	0.008
Classifications of LGE, n (%)				
None	24 (28)	15 (35)	9 (21)	
Infarct pattern	19 (22)	10 (23)	9 (21)	
Non-infarct pattern	33 (39)	14 (33)	19 (45)	0.34
Mixed	4 (5)	2 (5)	2 (5)	

Not done	5 (6)	2 (5)	3 (7)	
Presence of LGE n, (%)				
LGE present	56 (66)	26 (60)	30 (71)	0.188
LGE absent	24 (28)	15 (35)	9 (21)	
LGE not done	5 (6)	2 (5)	3 (7)	

Data as mean±SD, n (%). LA, left atrial; LGE, late gadolinium enhancement; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LVSV, left ventricular stroke volume; MR, mitral regurgitation; RVEDV, right ventricular end diastolic volume; RVEF, right ventricular ejection fraction

3.4.2 Cardiac reverse remodelling following TAVI

Following TAVI, all patients sustained a significant decrease in their mean aortic valve gradient from 41±16 mmHg to 18±10 mmHg ($p<0.001$) by CMR. At 6 months, compared to baseline, there were significant reductions in LV end-diastolic volumes ($p<0.001$), LV end-systolic volumes ($p=0.006$), and LV mass ($p<0.001$) (Table 2.3). Global LV and RV ejection fractions however did not change. In addition, LA volumes significantly reduced post-TAVI intervention (Table 2.3).

The 'significant' MR group had a greater degree of reduction in both MR regurgitant volumes (-19±14ml vs 1±13ml, $p<0.001$) and MR fraction (-17±13% vs 1±14%, $p<0.001$). No significant change in LV ejection fraction (0.2±8% vs 3±9%, $p=0.15$), RV ejection fraction (2±9% vs 1±9%, $p=0.54$) or LV mass (-32±19g vs -25±18g, $p=0.07$) were seen between groups. Those with significant MR experienced a greater reduction in LV end-diastolic ($p<0.001$) and end-systolic volumes ($p=0.04$) when compared to the 'non-significant' MR group (Figure 2.2).

Table 3.3 CMR parameters pre- and post TAVI interventions in all patients

All patients	**Baseline n=85**	**6m Follow up n=85**	**p value**
LV Mass (g)	138.2±35.3	109.9±31	<0.001
LVEDV (ml)	179±49.3	166.4±44.2	<0.001
LVESV (ml)	84.2±43.5	75.7±35.6	0.006
LVSV (ml)	94.5±22.5	90.7±18.7	0.04
LVEF (%)	54.8±12.2	56.3±10.6	0.10
RVSV (ml)	74.3±18.4	78.7±20.4	0.04
RVEF (%)	54.2±9.5	55.4±10.1	0.20
LA volume (ml)	131.8±45.0	119.1±41.3	<0.001
MR volume (ml)	22.4±15.0	13.7±12.9	<0.001
MR fraction (%)	22.6±13.3	14.5±12.4	<0.001
MR Classifications (n)			
Mitral regurgitation %			
MR none (0%)	8	14	
MR mild (5-15%)	20	35	
MR moderate (16-25%)	19	20	
MR moderate-severe (26-48%)	38	16	<0.001

Classifications of LGE, n (%)			
None	24 (28)	28 (33)	
Infarct pattern	19 (22)	23 (27)	
Non-infarct pattern	33 (39)	24 (28)	0.23
Mixed	4 (5)	3 (4)	
Not done	5 (6)	7 (8)	
Presence of LGE, n (%)			
LGE present	56 (66)	50 (59)	
LGE absent	24 (28)	28 (33)	0.43
LGE not done	5 (6)	7 (8)	

Data as mean±SD, n (%). LA, left atrial; LGE, late gadolinium enhancement; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LVSV, left ventricular stroke volume; MR, mitral regurgitation; RVEF, right ventricular ejection fraction; RVSV, right ventricular stroke volume

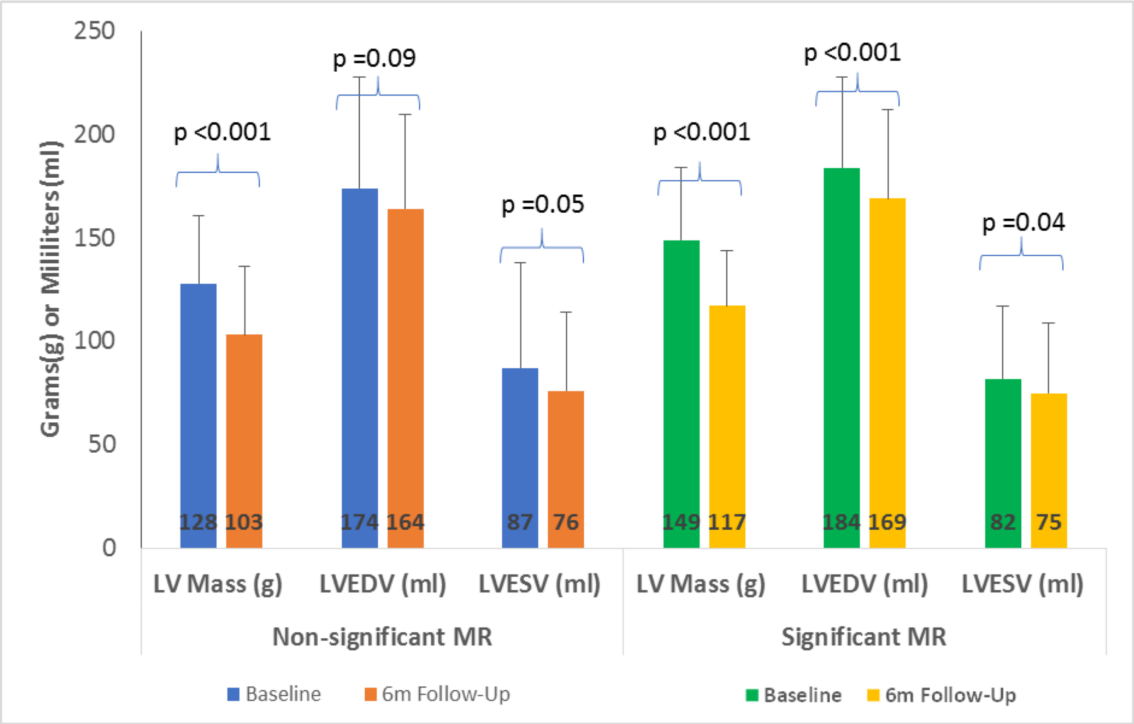

Figure 3.2 CMR characteristics at baseline and 6-months for 'Significant' and 'Non-significant' MR groups

LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; MR, mitral regurgitation. Error bars represent the 95% confidence interval.

3.4.3 Changes in MR fraction in the 'Significant MR' group

In those with significant MR at baseline (n=42), 77% (n=32) had a significant reduction in MR, moving them into the 'non-significant' category at 6 months, with an overall reduction in MR fraction from 34±6% to 17±14% (p<0.001) (Figure 2.3).

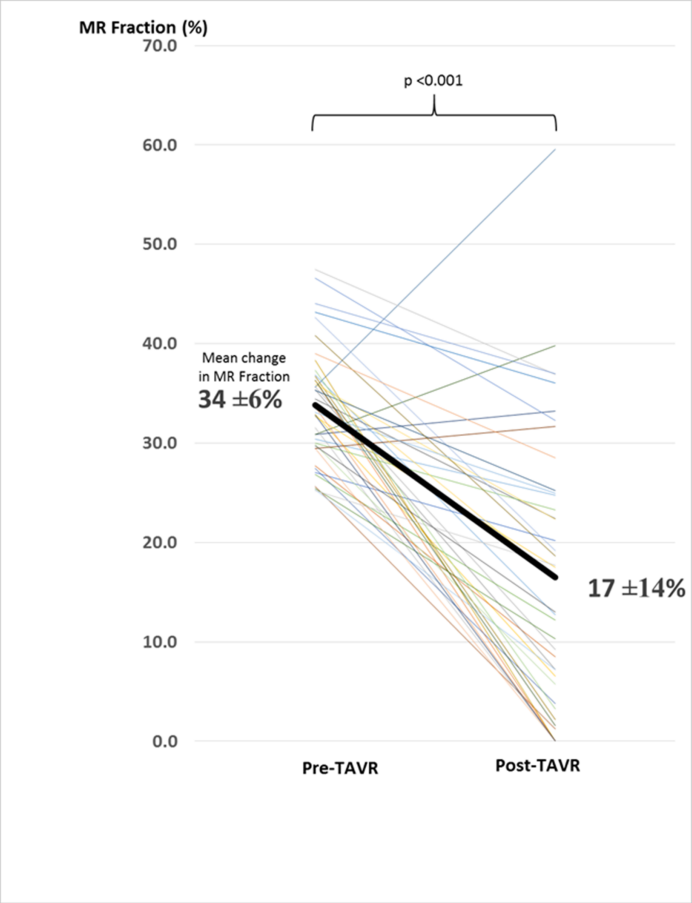

Figure 3.3 Change in MR Fraction (%) in the 'Significant MR' group post-TAVI

MR mitral regurgitant; TAVI, transcatheter aortic valve implantation

3.4.4 Changes in haemodynamics and cardiac reverse remodelling according to MR 'improver' and 'non-improver' status

From the total study population, MR significantly improved in 38% (n=32) of patients 6-months post-TAVI and worsened/unchanged in 62% (n=53) of patients. At follow up, the 'improvers' group, but not the 'non-improvers', had a significant improvement in LV stroke volume index (p=0.04) and a greater increase in aortic forward flow (p<0.001). Improvement in MR however was not associated with more favourable cardiac LV reverse remodelling compared with the 'non-improvers' (Figure 2.4).

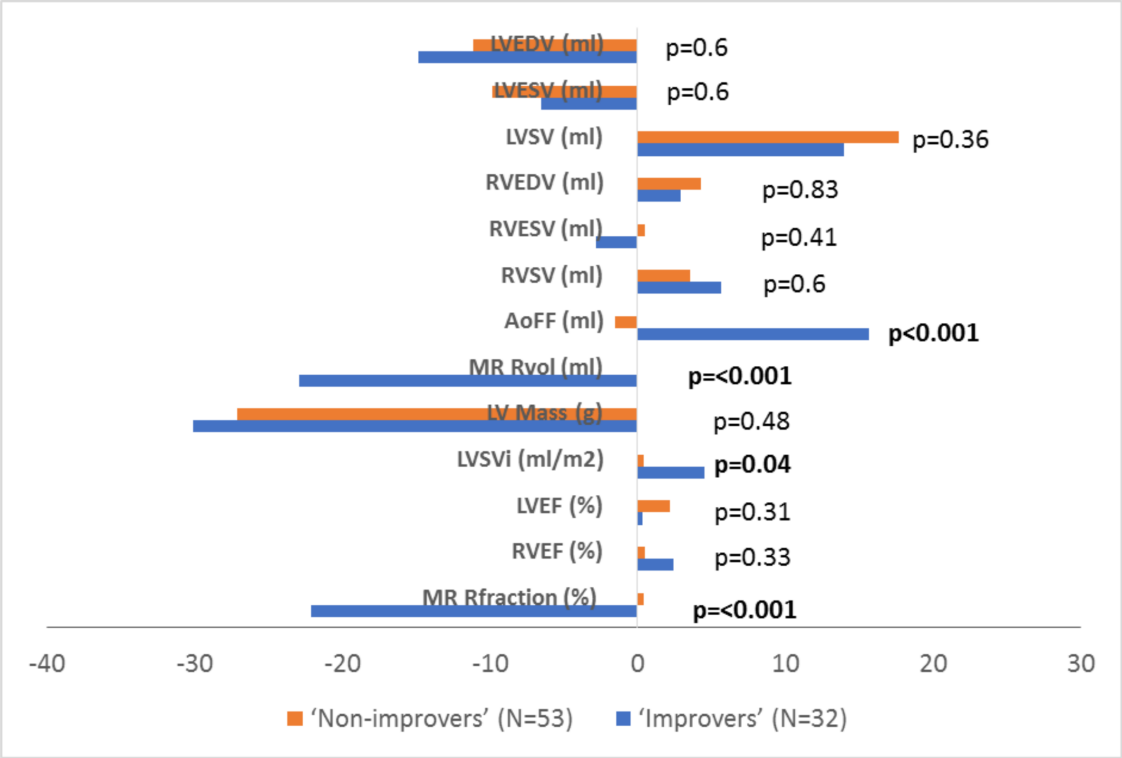

Figure 3.4 Change in cardiac reverse remodelling parameters in 'Improvers' and 'Non-improvers'

AoFF, aortic forward flow; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LVSV, left ventricular stroke volume; LVSVi, left ventricular stroke volume indexed; MR, mitral regurgitation; Rfraction, regurgitant fraction; RVESV, right ventricular end-systolic volume; RVEDV, right ventricular end-diastolic volume; RVEF, right ventricular ejection fraction; Rvol, regurgitant volume; RVSV, right ventricular stroke volume

In the 'improvers' group, 72% (n=23) had presence of LGE, 22% (n=7) had no LGE and LGE imaging was not performed in 6% (n=2) due to severe renal impairment. In those with LGE, the pattern of LGE was non-infarct pattern in 61% (n=14), infarct pattern in 35% (n=8), and mixed in 4% (n=1). The presence of LGE at baseline was associated with a greater reduction in MR fraction at 6-months following TAVI intervention (-11±16% versus 0.2±16%, p=0.01).

3.4.5 Other factors associated with MR improvement

Univariate regression analysis was conducted to look for any clinical or CMR factors associated with MR reduction following TAVI. The following variables were tested: baseline demographics, baseline and 6 months- LV and RV ejection

fraction, mass, and volumes; pre-treatment and post-treatment mean trans-aortic gradient (Table 2.4). A higher baseline RV ejection fraction or RV stroke volume, and a greater reduction in LV end-diastolic pressure (LVEDP) post-TAVI were all significantly associated with MR improvement. A lower aortic forward flow at baseline was also associated with the reduction in MR. Multivariate predictors of improved MR following TAVI intervention were pre-operative absence of atrial fibrillation, a higher RV stroke volume and a lower aortic forward flow at baseline.

3.4.6 Impact of MR on mortality

At a median of 3 (IQR 2.03-3.97) years follow-up, 24% (n=20) of TAVI patients had died. MR severity at baseline did not differ between those who died and those who did not; (mortality rate 13% vs 14%, non-significant vs significant, p=0.84) (Figure 2.5). Those who died also had a comparable reduction in MR severity post-TAVI (-7.3% vs -8.3%, p=0.81). Cumulative survival rates between the 'improvers' and 'non-improvers' did not differ at follow up (mean survival 5.5 years 95%CI 4.6-6.4 vs 5.5 years 95%CI 4.7-6.3, improvers vs non-improvers). Residual significant MR was also not associated with increased mortality.

Intra-observer variability for LV quantitation in this study was 1.6%, 3.6%, 3.0% and 1.8% for LV end-diastolic volume, LV mass, LV stroke volume and LV ejection fraction respectively; whilst the coefficient of variation for peak aortic flow velocity and aortic forward flow volume was 0.2% and 1.7%.

Table 3.4 Results of logistic regression for the improvement in MR post-TAVI

UNIVARIATE REGRESSION ANALYSIS Visit 1	R	R^2	F value	Standardised Co-efficient Beta	Beta CI Lower	Beta CI upper	Univariate P value
Sex	0.08	0.006	0.55	-0.08	-9.89	4.5	0.46
Age	0.03	0.001	0.11	0.03	-0.40	0.57	0.73
Logistic score	0.04	0.002	0.13	-0.04	-0.32	0.22	0.71
Euro II score	0.04	0.001	0.15	0.04	-0.65	0.97	0.69
STS mortality	0.17	0.02	2.53	-0.17	-2.15	0.23	0.11
STS morbidity	0.09	0.01	0.78	-0.09	-0.61	0.23	0.37
AF	0.29	0.08	8.17	-0.29	-20.4	-3.67	0.005
MI	0.12	0.014	1.23	0.12	-3.78	13.3	0.27
CABG	0.18	0.04	3.05	0.18	-0.93	14.5	0.08
PHT	0.003	<0.001	0.001	-0.003	-7.5	7.3	0.98
Change in LVEDP	0.20	0.04	3.17	0.21	-0.07	1.29	0.07

CMR characteristics							
LV Mass (g)	0.14	0.02	1.73	0.14	-0.03	0.16	0.19
LVEDV (ml)	0.05	0.003	0.27	0.05	-0.05	0.09	0.59
LVESV (ml)	0.006	< 0.001	0.003	0.006	-0.08	0.08	0.95
LVSV (ml)	0.11	0.013	1.09	0.114	-0.07	0.24	0.29
LVEF (%)	0.02	<0.001	0.05	0.02	-0.25	0.33	0.80
RVEDV (ml)	0.07	0.005	0.46	0.07	-0.06	0.13	0.49
RVESV (ml)	0.038	0.001	0.123	-0.038	-0.16	0.11	0.72
RVSV (ml)	0.20	0.04	3.59	0.20	-0.008	0.37	0.06
RVSVi (ml/m^2)	0.15	0.02	2.15	0.15	-0.09	0.61	0.14
RVEF (%)	0.18	0.03	2.89	0.18	-0.05	0.68	0.09
LA Volumes (ml)	0.06	0.004	0.33	-0.06	-0.10	0.05	0.56
Aortic valve parameters (CMR)							
Aortic FF (ml)	-0.338	0.013	11.4	-0.34	-0.49	-0.13	0.001

Ao Volume	0.45	0.20	12.17	-0.45	-0.8	-0.21	0.001
Ao Rfraction (ml)	0.35	0.12	11.8	0.35	0.32	1.22	<0.001
Aortic max PG (mmHg)	0.17	0.028	2.44	0.17	-0.04	0.39	0.12
Mean gradient, (mmHg)	0.21	0.04	2.12	0.21	-0.32	2.03	0.15
Ao peak vel (m/s)	0.20	0.04	2.08	0.20	-0.01	0.10	0.15
MR RVol (ml)	0.56	0.32	39.1	0.56	0.42	0.82	<0.001
MR Rfraction (%)	0.66	0.44	67.3	0.66	0.63	1.03	<0.001
VISIT 2 (Follow-up)							
Aortic valve parameters (CMR)							
Ao FF (ml)	0.39	0.15	15.1	0.39	0.18	0.56	<0.001
Ao Volume	0.46	0.21	13.62	0.46	0.19	0.65	<0.001
Ao Rfraction (ml)	0.16	0.02	2.31	-0.16	-1.04	0.13	0.132
Ao max PG (mmHg)	0.29	0.08	7.88	0.29	0.133	0.77	0.006

Mean gradient, (mmHg)	0.26	0.07	3.79	0.26	-0.04	2.77	0.05
Ao peak velocity (m/s)	0.32	0.10	5.6	0.32	0.01	0.16	0.02
RVSV (ml)	0.18	0.03	3.05	0.18	-0.02	0.32	0.08
RVEF (%)	0.27	0.07	6.58	0.27	0.09	0.78	0.01

AF, atrial fibrillation; CABG, coronary artery bypass graft; FF, forward flow; LA, left atrial; LVEDP, left ventricular end diastolic pressure; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LVSV, left ventricular stroke volume; MI, myocardial infarction; MR, mitral regurgitant; PG, pressure gradient; PHT, pulmonary hypertension; RFraction, regurgitant fraction; RVEDV, right ventricular end-diastolic volume; RVEF, right ventricular ejection fraction; RVESV, right ventricular end-systolic volume; RVol, regurgitant volume; RVSV, right ventricular stroke volume; RVSVi, right ventricular stroke volume(indexed); STS, Society of Thoracic Surger

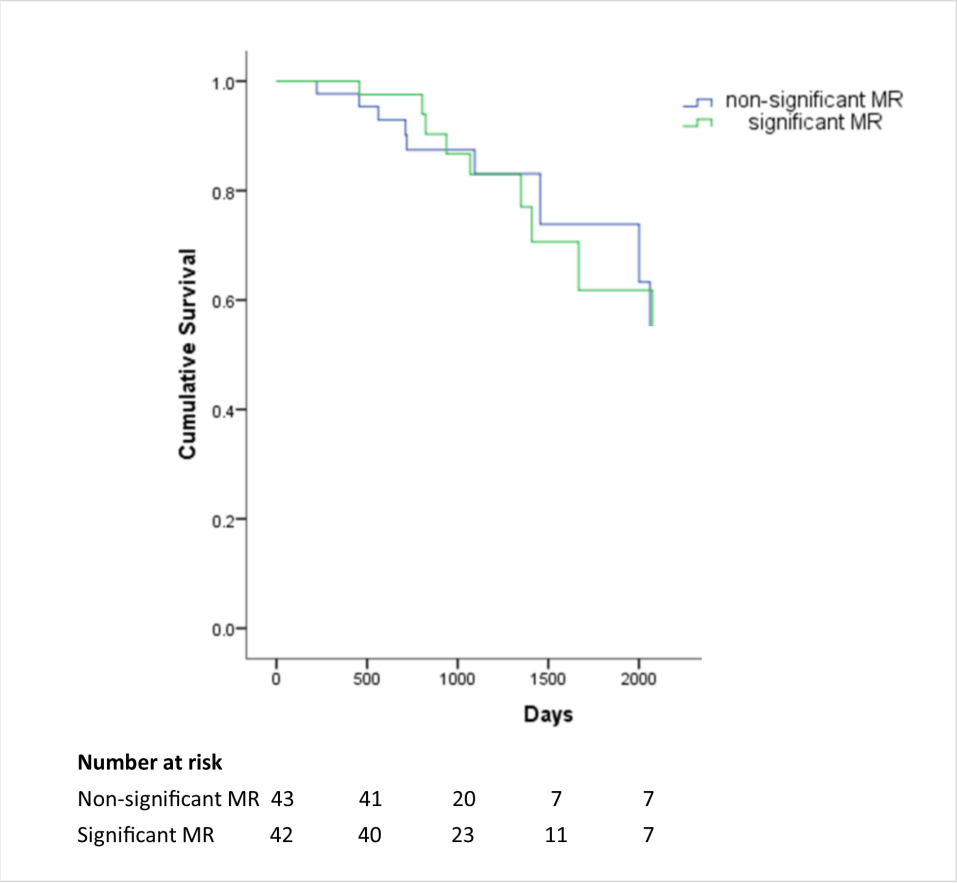

Figure 3.5 Kaplan Meier Curve for cumulative survival in 'significant' and 'non-significant MR' groups according to baseline status

Log rank p=0.94. MR, mitral regurgitation

3.5 DISCUSSION

This is the first CMR study to specifically assess MR in quantitative terms and evaluate its impact on cardiac reverse remodelling and mortality in patients undergoing TAVI. The main findings were 1) MR was shown to occur frequently in a TAVI population and those with 'significant MR' had a greater LV mass at baseline; 2) The presence of significant MR at baseline did not prevent LV reverse remodelling, as demonstrated by the substantial reduction in LV mass, LV diastolic and systolic volumes; 3) In those with significant MR at baseline, the MR is likely to improve following TAVI without the need for any specific intervention on the mitral valve; 4) The presence of LGE at baseline was

associated with a greater improvement in MR at 6-months post-TAVI; 5) Improvement in MR was neither associated with lower mortality nor more favourable cardiac reverse remodelling compared with the 'non-improvers'; 6) Baseline MR severity was not associated with long-term mortality.

Our findings are consistent with other large echocardiographic registries such as the Canadian Edwards SAPIEN registry (159), Italian CoreValve registry (164), and PARTNER Trial Cohort A study (165) demonstrating that TAVI is associated with a significant amelioration in MR severity. Although some studies suggested that significant MR results in an increase in mortality rates after TAVI (159,164,166,167), the findings in our study are consistent with others (158,161,165,168) which have not confirmed this association. Patients with a greater LV mass at baseline and higher aortic valve velocities (i.e. pressure-loaded ventricles) had a higher degree of MR in our study, likely due to raised LVEDP. We postulate that TAVI leads to the reduction of LVEDP and subsequently results in the amelioration of MR.

3.5.1 Aetiology of MR in severe aortic stenosis

A combination of MR aetiologies can be seen in many elderly patients who undergo TAVI and can explain the heterogeneous response in MR evolution after TAVI. The mechanisms of MR are usually classified as organic (a structurally abnormal mitral valve), or functional (leaflet coaptation deficit due to a change in left ventricular morphology(169). The additional marked increase in the LV-left atrial pressure gradient associated with severe AS can also contribute to increase the driving force through the regurgitant orifice area.

3.5.2 Pathophysiology: impact of TAVI on MR

In patients with aortic stenosis, LV hypertrophy and interstitial myocardial fibrosis are known sequelae of chronic pressure overload. The mechanism of improvement of concomitant significant MR in patients with severe AS can be multifactorial. The elimination of mechanical outflow obstruction through the aortic valve, with the subsequent reduction of the afterload reduces the

pathological retrograde flow through the mitral valve. LV cavity pressure drops very early after TAVI, and consequently, the trans-mitral pressure gradient may decrease, resulting in a reduction in MR (169). At later stages, regression of concentric myocardial hypertrophy due to the decrease in ventricular afterload and restoration of the proper geometry of the LV also leads to improved coaptation of the leaflets, hence improving MR which are mostly functional in aetiology (159,170–172).

3.5.3 Cardiac reverse remodelling following improvement of MR

Interestingly, we found that improvement in MR was neither associated with more favourable cardiac reverse remodelling nor lower mortality rates compared with the 'non-improvers'. There is however the possibility that a 6-month follow-up scan may have been too early to identify any difference in reverse remodelling between the groups.

3.5.4 Myocardial fibrosis

Chronic aortic valve disease is characterized by progressive accumulation of interstitial myocardial fibrosis (MF) (117). In response to the chronic pressure overload of severe AS, the LV reacts by compensatory hypertrophic remodelling in order to maintain cardiac output(119). Histologically, this translates to increased myocyte mass, expansion of the extracellular volume as well as increased fibrosis, leading to increased stiffness, impaired relaxation, and elevated LV filling pressure (116,170). Interestingly, this study found that the presence of LGE at baseline was associated with improvement in MR 6-months post-TAVI. A possible explanation is that patients with significant MR tend to have a more critical AS and a higher trans-valvular gradient, which inevitably results in a higher LV mass and myocardial replacement fibrosis, depicted as LGE. The greater alleviation of ventricular afterload in these patients following TAVI could result in greater LV mass regression and systolic atrioventricular gradient, leading to a greater degree of MR reduction.

3.5.5 Strength of methodology

A key strength of this study was the use of CMR to reliably quantitate MR volume with low intra- and inter-observer variabilities, irrespective of MR jet geometry (114,115). Previous TAVI studies have frequently used transthoracic echocardiography for MR assessment, which has limited reproducibility and relies on mathematical assumptions of LV geometry and cavity size, which may not apply in the remodelled ventricle. In fact, echocardiography, when compared to CMR, was found to overestimate MR severity in many patients (111). Some studies have also suggested that CMR is more accurate than echocardiography in assessing the severity of MR, especially in those with prolapsing leaflets and eccentric jets (129). Echocardiographic evaluation of MR severity requires integration of various qualitative and quantitative measurements (173). The variety of methods used for the quantitative assessment of MR may further explain the discrepancies amongst previous studies (159,165–168).

The presence of myocardial fibrosis has been reported to be an adverse prognostic marker in patients with AS, with a 6-8 fold increased mortality risk (117,174,175). Myocardial fibrosis has also been shown to adversely affect prognosis and functional outcomes following surgical aortic valve replacement (176), but as yet its role is not fully elucidated in a TAVI population. In a small study (n=20), the presence of LGE was found to predict higher cardiovascular mortality in patients with severe AS undergoing trans-femoral TAVI (116). The clinical impact of LGE, however, has never been assessed in the setting of concomitant MR in severe AS. We have shown that the presence of LGE was associated with an improvement in MR in the short term (6 months) following TAVI, although the mechanism for this remains undefined.

Despite excellent procedural success and outcomes following TAVI, issues remain regarding optimal patient selection. Decision-making in patients with significant MR in the context of severe AS is often complex. One option is to perform a double valve (aortic and mitral) surgical procedure, which might be considered too high-risk in this already high-risk population. The other option is to perform TAVI as a compromise solution, accepting non-treatment of concomitant MR with a potential negative impact on patient outcomes. Therefore, identifying patients with the highest and lowest likelihood for MR improvement

could be very important in the clinical decision-making process. LGE-CMR might allow clinicians to select patients who will most benefit from the TAVI procedure, obviating the need for high-risk double valve surgery. On the other hand, double-valve surgery may be more appropriate in patients with a low likelihood of MR improvement after TAVI. Although our small sample size did not demonstrate mortality benefits in those who improved their MR status, the literature to date has shown that MR improvement contributes to patient symptomatic improvement (177–179).

3.6 LIMITATIONS

The moderate sample size, short follow-up time frame and the single-centre study design limits the strength of our conclusions. However, comparisons between the two groups using the highly reproducible technique of CMR meant it was appropriately powered for LV reverse remodelling parameters. The exclusion of patients with pacemakers (7%), severe AR and inclusion of survivors only in the CMR analysis raises the potential for selection bias. The analysed population however did not differ in terms of baseline characteristics from the original whole study population. Because we excluded patients with contraindications to CMR and specific medical conditions, our study population is highly selected and so our conclusions cannot be extrapolated to all patients with severe AS.

Additionally, our study had a high proportion of patients with atrial fibrillation (20%), an arrhythmia which could reduce the quality of image acquisition and therefore reduce the accuracy of volumetric quantification with CMR. MR fraction in the context of severe AS may be overestimated using CMR phase contrast imaging due to underestimation of aortic forward flow when sampling high velocities. When performing phase contrast-based flow measurements in patients with heart valve replacement, there is also a potential for flow and volume miscalculation due to prosthesis-related distortions of the magnetic field (180). Confounders such as primary or ischemic aetiology, change in medications and development of bundle branch block or aortic regurgitation could additionally impact on cardiac reverse remodelling following TAVI. Finally, quantification of

fibrosis on LGE images were analysed using a semi-automatic, signal intensity threshold method rather than the newer T1 mapping techniques, as the latter were not widely employed at the time of patient recruitment.

3.7 CONCLUSION

Significant MR is common in patients undergoing TAVI and improves in the majority post-procedure. Improvement in MR was not associated with LV reverse remodelling and baseline MR severity was not associated with mortality.

Chapter 4 Assessment of left ventricular reverse remodelling following mitral valve repair and mitral valve replacement in degenerative mitral regurgitation: a cardiovascular magnetic resonance study

4.1 ABSTRACT

Introduction

Mitral valve (MV) repair is currently recommended over replacement. The guidelines suggesting this are however based on historic evidence which compared outdated techniques of MV replacement. Recent data cast doubts on its validity in the current era of chordal-preservation techniques in MV replacement.

Aims

Using CMR imaging, this study aimed to assess the impact of MV repair and MV replacement on cardiac reverse remodelling.

Methods

65 patients with significant degenerative mitral regurgitation (MR) were prospectively recruited. Of these, 37 patients (59% men, 65±15years) to date with paired CMR scans at baseline and 6 months were evaluated for this thesis. Patients were either undergoing MV repair (n=9), MV replacement (n=10) or treated with optimal medical management (n=18). The CMR protocol included cines for left ventricle (LV), left atria (LA), and aortic flow assessment. The LA and LV parameters, and MR severity were analysed and patients were followed up for a median duration of 7.2months (IQR 6.0-8.2).

Results

At 6months, both the repair and replacement groups exhibited a greater reduction in LV end-diastolic volume and LA volumes when compared to the control group. The indexed LVEDV decreased significantly from 129±33ml to 99±37ml, p<0.001 in the repair group, from 118±24ml to 90±26ml, p<0.001 in the replacement group and remained unchanged in the control group 115±25ml to 113±25ml, p=0.53. The absolute reduction in indexed LVEDV was not significantly different between the repair and replacement groups (-30±15ml vs -29±19ml, repair vs replacement, p=1.00). Similarly, both surgical groups also sustained an equal degree of LA size reduction (-42±26ml/m^2 vs -36±23ml/m^2, repair vs replacement; p= 1.00). There was a decline in the global postoperative LV ejection fraction. The degree of reduction in LV ejection fraction however did not differ between the repair and replacement group (-9±6% vs -6±8%, repair vs replacement; p=1.00). Those undergoing surgery experienced a significant reduction in their MR severity, although those with replacement had a more effective reduction of MR volume (MR fraction for repair: 47±9% to 15±10%, p<0.001 vs replacement: 41±13% to 5±4%, p<0.001).

Conclusion

MV surgery leads to positive atrial and left ventricular reverse remodelling, and a decline in global LV ejection fraction. In this small series, MV replacement with chordal preservation showed similar cardiac reverse remodelling benefits to MV repair. Although residual MR is often seen following repair, this did not lead to a less favourable cardiac reverse remodelling in this small patient population.

4.2 INTRODUCTION

Mitral regurgitation is the second most prevalent valve lesion requiring surgery in the developed world (2) and is associated with significant 5 year mortality(1). Surgical valve repair is currently recommended over replacement in degenerative disease (29,181) as it is thought to be associated with a more favourable reverse remodelling response(182), greater freedom from prosthesis related complications and a lower post-operative mortality(32,183–185). However, the guidelines suggesting this use historic evidence(34,183,186) which pre-date recent advances in MV replacement with chordal preservation, which has an important impact on cardiac reverse remodelling (187,188).

Foundational evidence from which these guidelines are based on are rather weak, and derived largely from non-randomised, single-centre, observational studies which are unavoidably prone to selection bias, with the replacement population typically being higher surgical risk. Other studies used crude multivariate adjustment statistical methods to control for differences in baseline characteristics between patient groups(36,189–192). These studies were also conducted in an era when operative mortality was still high and chordal preservation technique was not a routine, potentially adversely affecting left ventricular geometry and function(193). Recent data comparing MV repair and replacement failed to demonstrate superiority of repair in specific subgroups such as degenerative disease(186,190,194), women(195), patients with endocarditis(196) or in those with an ischaemic aetiology(42,197).

The most commonly (and easily repaired) organic leaflet pathology is that of P2 segment prolapse, but any scallop or combination of scallops can be affected. Importantly, all but the simplest of MV repairs are technically more complex(184) and are associated with longer cardiopulmonary bypass times(198,199), potentially increasing risk of cerebral embolic load(200) and affecting functional capacity and quality of life. Late failure of the repair also often results in reoperation that carries an associated morbidity and mortality(34,201,202). MV

replacement techniques have developed over the last decade (7) and newer generation mechanical prostheses, with enhanced flow characteristics and reduced thromboembolic potential, may be associated with better outcomes(203). This has certainly highlighted the need to clarify the evidence behind MV repair versus replacement, especially in this modern era of newer replacement techniques of chordal-preservation. It may be that MV replacement with modern chordal preservation techniques (started in late 1980s) does not impact less favourably on LV reverse remodelling degenerative MR.

Accurate assessment of MR severity and its complications are important, as it carries significant prognostic implications(3,5,121,204). There are however few robust imaging studies in the contemporary surgical era comparing these two techniques. The commonly used two-dimensional echocardiography to evaluate LV volumes are based on geometric assumptions and the quantitation of MR can also be challenging in patients with MV prolapse(173,205) due to its non-holosystolic eccentric jet. CMR is more accurate and reproducible in ventricular volumes assessment (48,206) and has the additional ability to quantify MR with high accuracy and reproducibility (irrespective of MR jet geometry) using a combination of LV volumetric measurements and aortic flow quantification (112–114,121,128,136). Some studies have suggested that CMR is more accurate than echocardiography in assessing the severity of MR, especially in those with prolapsing leaflets and eccentric jets (129,204). Recent work has further confirmed that quantitative CMR measurements of regurgitation volume correlate better with outcomes (121,129,204).

We hypothesized that in the era of MV replacement with chordal preservation, there would be no difference between MV repair and replacement in the degree of cardiac reverse remodelling at 6months postoperatively. The objectives of this study were therefore to: 1) to investigate LV reverse remodelling following mitral valve repair and mitral valve replacement; 2) to assess post-operative changes in LA volumes 3) to quantitate the change in MR severity between both surgical groups, compared to a group of patients under watchful waiting.

4.3 METHODS

4.3.1 Study design and population

Between February 2016 and May 2018, 65 patients with significant MR were prospectively recruited from the cardiology and cardiac surgery out-patient departments at a single tertiary centre, Leeds Teaching Hospitals NHS Trust, Leeds, UK. Inclusion criteria included: moderate-severe or severe degenerative MR on echocardiography accepted for mitral valve repair (Group 1), mitral valve replacement (Group 2) or a watchful waiting/ medical management approach (Group 3), age >18 years, capacity and willingness to consent to participation and ability to perform all components of the study protocol. Exclusion criteria were as described in Chapter 2. The patient recruitment pathway can be seen in Figure 3.1 and only those with paired CMR scans (n=37) were analysed in this study. Patients with concomitant coronary artery bypass graft (CABG), concomitant tricuspid valve intervention, atrial MR (annular dilatation) or pacemaker insertion were excluded from the final analysis. Patients were either undergoing MV repair (n=9), MV replacement (n=10) or treated with optimal medical management (n=18). Decision for MV intervention was taken by a multidisciplinary heart team in accordance with international guidance. Baseline clinical and demographic data were recorded for all patients. CMR scans were performed at baseline and either at 6-months post-MV intervention (MV repair or replace) or 6-months after follow-up scan (medical management). Clinical teams were blinded to CMR data. All patients provided written informed consent. 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).

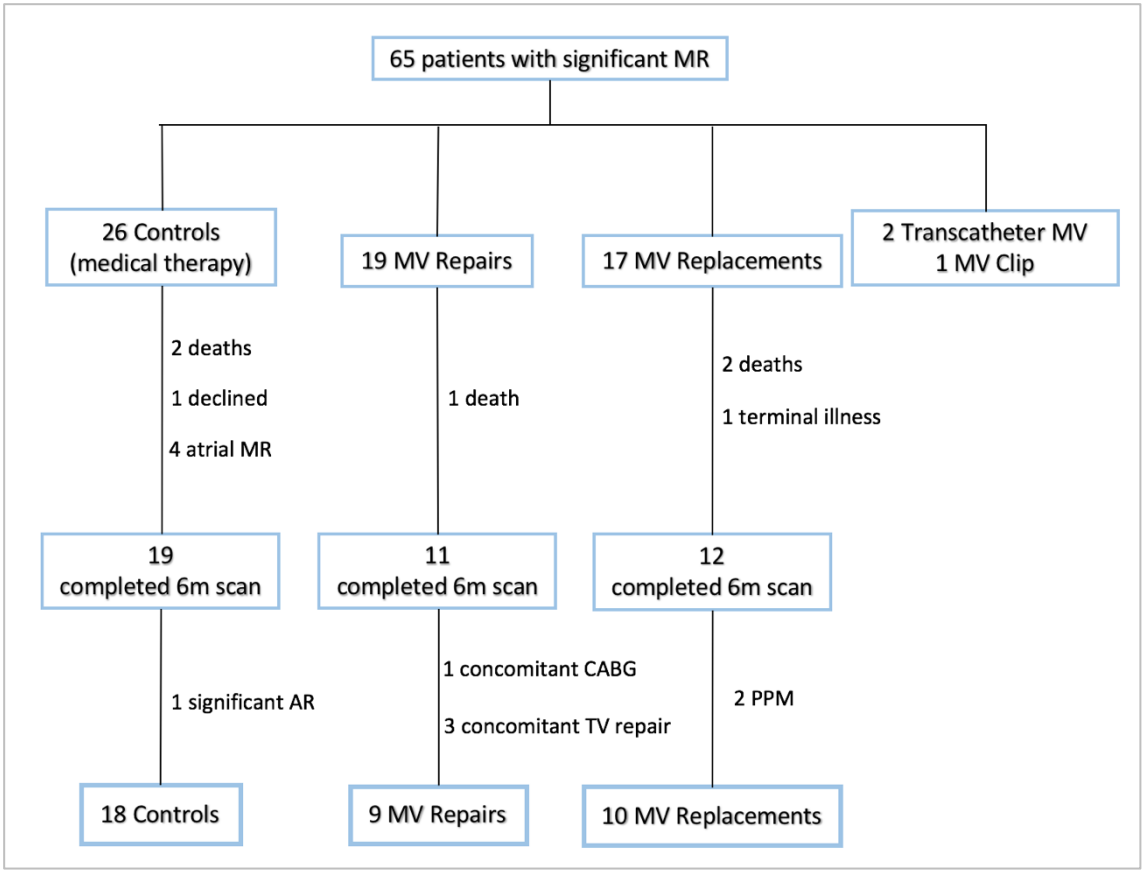

Figure 4.1 Patient recruitment pathway

MR, mitral regurgitation; MV, mitral valve; AR, aortic regurgitation; CABG, coronary artery bypass graft; TV, tricuspid valve; PPM, permanent pacemaker; atrial MR: mitral regurgitation with atrial annular dilatation.

4.3.2 Mitral valve intervention

Patients underwent a standard work-up for MV intervention which included TOE and pre-operative right and left heart catheterisation. MV surgery was performed under general anaesthesia using a standard technique of cardiopulmonary bypass via a 7-10 cm midline sternotomy incision and mild systemic hypothermia (30-34°C). Intra-operative TOE was also utilised. Systemic heparinisation followed by aorto-bicaval cannulation ensued and LA incision was made to expose the pathological MV. All MV repairs were performed with the Gore-Tex chordae sutures and supported with a Carpentier-Edwards Physio II annuloplasty ring, typically 29-34mm in size. Conversely, MV replacements were performed using either the St Jude mechanical valve or the St Jude Epic^{TM} Mitral stented tissue valve with Linx^{TM} AC technology, typical size of 27-33mm. All MV replacements preserved the posterior chordopapillary apparatus (i.e. partial chordal sparing). The technique of preservation, type of prosthetic valve and

technique of suture placement were at the discretion of the surgeon. Procedures were performed by either one of the three experienced, high-volume cardiac surgeons in our centre. All patients received protamine prior to closure of wound with Myowires over mediastinal drains. Patients with mechanical valves were treated with life-long anticoagulation (Vitamin K antagonist-warfarin) after the procedure.

4.3.3 CMR protocol and image acquisition

Identical baseline and 6-month follow-up scans were performed on a 1.5T MRI system (Intera, Phillips Healthcare, Best, Netherlands). A blood pressure (BP) cuff was placed on the left arm and pre-scan BP readings were recorded. The heart CMR protocol comprised of: 1. Scout images to determine LV short axis and LVOT 2. Multi-slice, multi-phase cine imaging covering the entire LV in short axis plane using a standard balanced steady-state free precession pulse sequence (TR 3msec, TE 1.6msec, flip angle 60°, SENSE factor 2, 10mm thickness, 0mm gap, spatial resolution 1.2 x 1.2 x 10mm^2, 30 phases, matrix 192x131, voxel size 1.88x1.88mm , typical FOV 340mm) 3. Cine imaging of a standard 4-chamber, 2-chamber, and two orthogonal LVOT views in sagittal-oblique and coronal views to allow planning of aortic valve Q-flow imaging. 3. Through-plane velocity encoded phase contrast imaging at the aortic sino-tubular junction, orthogonal to the aortic valve jet (VENC 150–350cm/s, retrospective gating, slice thickness 8mm, 30 phases, FOV 340mm). VENC was typically set at 150 cm/s. If aliasing occurred at the pre-set VENC, sequential phase contrast imaging was performed at increasing VENC settings until the aliasing artefact had disappeared. Other scan parameters for gradient echo phase contrast (PC) imaging were as follows: typical FOV 350x280mm, TR 5.1msec, TE 3.2msec, flip angle 15°, temporal resolution 28msec, number of signal averages 1, SENSE factor 2, turbo field echo (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.

4.3.4 CMR Analysis

CMR analysis was performed by an independent operator (PC). Ventricular volumes, LV mass, left atrial volume and MR fraction (%) were calculated based on the general methodology described in Chapter 2.

4.3.5 Statistical Analysis

General statistical analysis were as described in Chapter 2. Analysis of variance (ANOVA) test with Bonferroni correction was employed to compare data between controls, repair and replacement groups. Due to the relatively small sample size, the Fisher's exact test (instead of Chi-squared test) was used for comparing categorical variables. Two-sided P values <0.05 were considered statistically significant.

4.4 RESULTS

4.4.1 Overall patient characteristics

Of 65 patients with significant MR, 37 patients (59% men, age 65±15years, BMI 24.3±3.5 kg/m^2 and BSA 1.9±0.2m^2) with paired CMR scans were included in the final data analysis for this thesis. Aetiology of MR was posterior mitral valve leaflet prolapse in 22/37 patients (60%), anterior mitral valve leaflet prolapse in 4/37 patients (11%), bi-leaflet prolapse in 9/37 patients (24%) and flail leaflet in 2/37 patients (5%). Baseline systolic and diastolic BP was 123±20mmHg and 72±13mmHg respectively, and patients had a mean 6-minute walk test length of 362±103meters. A high proportion of patients (35%) had AF and majority of the recruited cohort (76%) were in NHYA Class I-II. Patients were either undergoing MV repair (n=9), MV replacement (n=10) or treated with optimal medical management (n=18). Of those who underwent MV replacement, 7 patients had mechanical valves whereas bio-prosthetic valves were implanted in 3 other patients. Median time of follow up was 7.2months (IQR 6.0-8.2). Basic demographics and clinical data for all clinical patients can be seen in Table 3.1.

Table 4.1 Baseline demographics in all patients

	All patients (n= 37)
Age (years)	65±15
Male sex, n (%)	22 (59)
Logistic Euroscore	5.2±5.2
Euroscore II	1.6±1.5
STS mortality	1.7±1.8
STS morbidity	13.5±7.8
Smoker	2(5)
Diabetes mellitus	3(33)
Hypertension	5(14)
Atrial fibrillation	13(35)
Myocardial Infarction	2(5)
Previous PCI	2(5)
CVA	1(3)
COPD	4(11)
CKD	2(5)
Bloods	
Haemoglobin (g/L)	135±14
Pack cell volume (L/L)	0.41±0.03
Creatinine (µmol/L)	84±22
NHYA Class	
Class I-II	28(76)
Class III	9(24)
Medications	
Aspirin	7(19)
Clopidogrel	0(0)
Beta-blocker	15(41)
Statin	13(35)

ACE-inhibitor/ARB	20(54)
Aldosterone antagonist	1(3)
Frusemide	14(38)
Calcium channel blocker	4(11)
Digoxin	4(11)
Amiodarone	2(6)
Metformin	1(3)
Insulin	0(0)
Anticoagulation	12(32)

Data as mean±SD, n (%). STS, Society of Thoracic Surgery; PCI, percutaneous coronary intervention; CVA, cerebrovascular accident; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; NHYA, New York Heart Association, ACE-I, Angiotensin converting enzyme inhibitor; ARB, angiotensin renin blocker

4.4.2 Baseline CMR data for all patients

CMR data for all clinical patients are described in Table 3.2. Mean baseline LV ejection fraction was 56±6%, MR volume 47±19ml and MR fraction 39±12%. According to CMR criteria for MR classification (112), MR was graded as severe in 29/37 patients (78%), moderate-severe in 8/37 patients (22%), moderate in 5/37 patients (14%) and only mild in 1/37 patients (3%). In those patients with mild or moderate range of MR severity, 5 patients were in the medical management group, and 1 patient was in the surgical group. Consistent with volume overload and its related consequences, baseline indexed LV end-diastolic volume was increased at 119±27ml/m^2 and LA volume index was elevated at 88±25 ml/m^2.

Table 4.2 Baseline CMR characteristics of patients in all patients

Cardiovascular variables	All patients
LV Mass (g)	97±25
LV Mass index (g/m^2)	52±11
LVEDV (ml)	221±52
LVEDV (indexed), ml/m^2	119±27
LVESV (ml)	96±31
LVESV (indexed), ml/m^2	52±16
LVSV (ml)	121±26
LVSV (indexed), ml/m^2	66±13
LVEF (%)	56±6
LV cardiac output, ml/min	8460±1558
LV cardiac index, ml/min/m^2	4599±851
LA volume (ml)	163±47
LA volume index (ml/m^2)	88±25
Aortic Flow	
Ao forward flow (ml)	69±20
Ao backward flow (ml)	4±3
Ao volume (ml)	65±20
Ao RF (%)	6±4
Ao max PG (mmHg)	7.8±4.0
Ao mean PG (mmHg)	1.5±0.7
Ao peak velocity (m/s)	1.4±0.3

Data as mean±SD. LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVSV, left ventricular stroke volume; LVEF, left ventricular ejection fraction; LV, left ventricle; LA, left atrial; Ao, aortic; RF, regurgitant fraction; PG, pressure gradient; MR, mitral regurgitation.

4.4.3 Baseline demographics for repair vs replace vs controls

Patients in all the 3 groups were well balanced and matched for age, gender, body mass index (BMI), surgical risk scores, co-morbidities and valve severity (Table 3.3). As expected, majority of those amenable to MV repair (89%) were of posterior mitral valve leaflet prolapse in origin. Patients in the intervention group had a higher proportion of patients with symptoms, 33% of repair and 50% of

replacement and only 6% of those in the control group were of NHYA Class III. Despite the difference in NHYA classifications, there was no significant differences in their 6-minute walk test. Although not statistically significant, those undergoing surgery are more likely to have MR in the severe end of the spectrum. The use of cardiovascular medications was similar across the 3 groups.

4.4.4 Baseline CMR data for repair vs replace vs controls

The mean LV ejection fraction at baseline was 59±5% in the controls, 54±7% in the repair group, and 55±7% in the replacement group. Although those in the surgical group (MV repair and MV replacement) had a higher LV end-diastolic volume, LV end-systolic volume and LA volume; and a lower LV ejection fraction and aortic forward flow volume, this was not statistically different from those in the control group (Table 3.4). Those undergoing MV repair also tended to have larger LV volumes at their baseline scan although this was not statistically different from those of controls/replacement. On the whole, no significant difference existed between the groups' pre-operative indexed measurements: end-diastolic volume, end systolic volume, stroke volume, LV mass and LV ejection fraction. LV cardiac output/index also did not differ between the groups. Those in the repair group had a higher MR volume and fraction when compared to the control group (when quantified by CMR). There were however no significant differences in MR volume and MR fraction between the repair and the replacement group. Those in the repair group also appeared to have a higher degree of aortic regurgitation fraction (5.2±4.1% vs 9.0±3.2% vs 5.5±2.8%, controls vs repair vs replacement, p value of controls vs repair = 0.04).

Table 4.3 Baseline demographics in 'Controls', 'Repair' and 'Replacement' groups

	Controls (n=18)	Repair (n=9)	Replacement (n=10)	P value (Controls vs Repair)	P value (Repair vs Replace)	P value (Controls vs Replace)	P value between groups
Age	66±17	64±14	68±11	1.00	1.00	1.00	0.87
Male sex, n (%)	9(50)	7(78)	6(60)				0.42
BMI	23.9±3.4	26±4	24±3	0.84	1.00	1.00	0.51
BSA	1.8±0.2	1.9±0.2	1.9±0.2	1.00	1.00	1.00	0.67
Systolic BP	125±26	118±13	125±14	1.00	1.00	1.00	0.66
Diastolic BP	72±15	69±13	75±10	1.00	1.00	1.00	0.69
6MWT	376±121	335±114	360±46	1.00	1.00	1.00	0.63
Logistic Euroscore	6.8±7	3.5±2.3	4.1±2.1	0.38	1.00	0.59	0.22
Euroscore II	1.6±1.8	1.3±0.7	1.8±1.4	1.00	1.00	1.00	0.73
STS mortality	2.0±2.2	1.1±1.2	1.9±1.6	0.76	1.00	1.00	0.49
STS morbidity	14.1±8.6	10.3±5.9	15.1±8	0.73	0.60	1.00	0.38
Smoker	0(0)	1(11)	1(10)				0.62
Diabetes	2(11)	0(0)	1(10)				0.36
Hypertension	4(22)	1(11)	0(0)				0.27
Atrial fibrillation	4(22)	4(44)	5(50)				0.13
Myocardial Infarction	1(6)	0(0)	1(10)				1.00
PCI	1(6)	0(0)	1(10)				1.00

CVA	1(6)	0(0)	0(0)				1.00
COPD	3(17)	1(11)	0(0)				0.66
CKD	1(6)	0(0)	1(10)				1.00
Bloods							
Haemoglobin (g/L)	134±12	136±17	136±16	1.00	1.00	1.00	0.86
Pack cell volume (L/L)	0.40±0.03	0.41±0.05	0.41±0.05	1.00	1.00	1.00	0.86
Creatinine (µmol/L)	75±14	96±29	90±22	0.05	1.00	0.23	**0.03**
MR Aetiology							
PMVL prolapse	10(56)	8(89)	4(40)				
AMVL prolapse	1(6)	0(0)	3(30)				
Bi-leaflet prolapse	5(28)	1(11)	3(30)				
Flail	2(11)	0(0)	0(0)				
Valve Severity (Echo)							0.10
Moderate-severe	6(33)	2(22)	0(0)				
Severe	12(67)	7(78)	10(100)				
NHYA Class							
Class I-II	17(94)	6(67)	5(50)				**0.01**
Class III	1(6)	3(33)	5(50)				**0.01**
Medications							
Aspirin	2(11)	1(11)	4(40)				0.19

Clopidogrel	0(0)	0(0)	0(0)				n/a
Beta-blocker	6(33)	4(44)	5(50)				0.68
Statin	5(28)	2(22)	6(60)				0.17
ACE-i /ARB	10(56)	5(56)	5(50)				1.00
Aldosterone antagonist	0(0)	1(11)	0(0)				0.24
Frusemide	6(33)	5(56)	3(30)				0.51
CCB	2(11)	1(11)	1(10)				1.00
Digoxin	2(11)	1(11)	1(10)				1.00
Amiodarone	1(6)	0(0)	1(10)				1.00
Metformin	0(0)	0(0)	1(10)				0.51
Insulin	0(0)	0(0)	0(0)				n/a
Anti-coagulation	4(22)	4(44)	4(40)				0.47

Data as mean±SD, n (%). ANOVA with Bonferroni correction was used to compare continuous data between groups, whereas Fisher's exact test was used to compare binary data between groups. STS, Society of Thoracic Surgery; PCI, percutaneous coronary intervention; CVA, cerebrovascular attack; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; PMVL posterior mitral valve leaflet; AMVL, anterior mitral valve leaflet; NHYA, New York Heart Association, ACE-I, Angiotensin converting enzyme inhibitor; ARB, angiotensin renin blocker; CCB, Calcium channel blocker

Table 4.4 Baseline CMR characteristics of patients in Controls, 'Repair' and 'Replacement' groups

Cardiovascular variables	Controls (n=18)	Repair (n=9)	Replace (n=10)	P value (Controls vs Repair)	P value (Repair vs Replace)	P value (Controls vs Replace)	P value ANOVA between groups
LV Mass (g)	95±20	103±25	97±33	1.00	1.00	1.00	0.73
LV Mass index (g/m^2)	52±10	54±13	52±14	1.00	1.00	1.00	0.88
LVEDV (ml)	209±46	244±57	220±58	0.32	0.98	1.00	0.27
LVEDV (indexed), ml/m^2	115±25	129±33	118±24	0.63	1.00	1.00	0.44
LVESV (ml)	85±23	115±38	100±32	0.05	0.84	0.60	0.05
LVESV (indexed), ml/m^2	46±12	61±22	54±14	0.08	0.90	0.77	0.08
LVSV (ml)	118±21	129±24	120±34	1.00	1.00	1.00	0.61
LVSV (indexed), ml/m^2	65±11	68±14	64±15	1.00	1.00	1.00	0.80
LVEF (%)	59±5	54±7	55±7	0.17	1.00	0.36	0.10
LV cardiac output, ml/min	8264±1517	8798±1410	8511±1845	1.00	1.00	1.00	0.70
LV cardiac index, $ml/min/m^2$	4564±858	4642±823	4625±947	1.00	1.00	1.00	0.97
LA volume (ml)	146±38	174±40	181±60	0.40	1.00	0.18	0.11
LA volume index (ml/m^2)	81±22	92±22	98±32	0.87	1.00	0.28	0.21

Aortic Flow							
Ao forward flow (ml)	75±20	63±20	66±21	0.47	1.00	0.80	0.29
Ao backward flow (ml)	3.9±4.0	5.3±1.7	3.5±2.2	0.92	0.68	1.00	0.44
Ao volume (ml)	71±19	58±20	63±21	0.30	1.00	0.82	0.22
Ao RF (%)	5.2±4.1	9.0±3.2	5.5±2.8	**0.04**	0.12	1.00	**0.03**
Ao max PG (mmHg)	8.8±4.8	6.8±1.6	7.1±3.6	0.62	1.00	0.79	0.34
Ao mean PG (mmHg)	1.6±0.8	1.5±0.6	1.4±0.8	1.00	1.00	1.00	0.81
Ao peak velocity (m/s)	1.5±0.4	1.3±0.2	1.3±0.3	0.70	1.00	0.73	0.35
Mitral regurgitation							
MR volume (ml)	39±14	60±13	50±25	**0.01**	0.63	0.34	**0.02**
MR fraction (%)	33±12	47±9	41±13	**0.01**	0.79	0.28	**0.02**

Data as mean±SD. ANOVA with Bonferroni correction was used to compare continuous data between groups. LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVSV, left ventricular stroke volume; LVEF, left ventricular ejection fraction; LV, left ventricle; LA, left atrial; Ao, aortic; RF, regurgitant fraction; PG, pressure gradient; MR, mitral regurgitation.

4.4.5 6-months CMR data for repair vs replace vs controls

At 6 months, no significant between-group differences existed in the assessment of LV end-diastolic volume or LV mass (Table 3.5). LV stroke volume and LV cardiac output were significantly lower in those who had surgery. The post-operative LV stroke volume was however similar in the repair and replacement groups (p=1.00). Although a lower post-operative LV ejection fraction was seen in the surgical groups, no significant differences were observed between the repair and replacement groups (repair 45±8% vs replacement 49±9%, p=0.86).

No differences in aortic flow parameters were observed amongst all groups. The repair group had a lower LA volume at follow-up scan, but this was not statistically different from the replacement group. A lower degree of MR volume and MR fraction was observed in both the surgical groups postoperatively (MR fraction: 32±14% vs 15±10% vs 5±4%, control vs repair vs replacement, respectively). Although residual MR volume was higher in the repair group (13±8ml vs 4±3ml, repair vs replacement; p=0.62) this was not statistically significant.

Table 4.5 CMR characteristics of patients in Controls, 'Repair' and 'Replacement' groups during 6 months follow-up scan

Cardiovascular variables	Controls (n=18)	Repair (n=9)	Replace (n=10)	P value (Controls vs Repair)	P value (Repair vs Replace)	P value (Controls vs Replace)	P value ANOVA Btwn groups
LV Mass (g)	94±20	92±33	90±35	1.00	1.00	1.00	0.93
LV Mass index (g/m^2)	51±9	49±18	48±15	1.00	1.00	1.00	0.75
LVEDV (ml)	204±46	187±66	168±60	1.00	1.00	0.30	0.25
LVEDV (indexed), ml/m^2	113±25	99±37	90±26	0.74	1.00	0.13	0.12
LVESV (ml)	86±28	108±56	89±47	0.63	0.98	1.00	0.43
LVESV (indexed), ml/m^2	47±15	57±31	47±22	0.85	0.98	1.00	0.51
LVSV (ml)	118±23	80±15	79±19	**<0.001**	1.00	**<0.001**	**<0.001**
LVSV (indexed), ml/m^2	65±13	42±7	43±8	**<0.001**	1.00	**<0.001**	**<0.001**
LVEF (%)	58±6	45±8	49±9	**<0.001**	0.86	**0.007**	**<0.001**
LV cardiac output, ml/min	7932± 1844	5801± 1018	5517± 1493	**0.007**	1.00	**0.001**	**<0.001**

LV cardiac index, ml/min/m²	4383±1023	3069±643	2955±629	**0.001**	1.00	**<0.001**	**<0.001**
LA volume (ml)	152±50	94±45	114±39	**0.01**	1.00	0.13	**0.01**
LA volume index (ml/m²)	85±29	50±23	62±18	**0.005**	0.92	0.08	**0.004**
Aortic Flow							
Ao forward flow (ml)	77±22	64±12	72±18	0.31	1.00	1.00	0.26
Ao backward flow (ml)	4.1±4.4	3.2±1.7	3.4±2.4	1.00	1.00	1.00	0.77
Ao volume (ml)	73±23	61±12	67±17	0.38	1.00	1.00	0.30
Ao RF (%)	5.8±5.3	5.2±3.4	4.9±3.6	1.00	1.00	1.00	0.86
Ao max PG (mmHg)	8.3±5.2	6.3±2.1	7.0±3.3	0.73	1.00	1.00	0.45
Ao mean PG (mmHg)	1.6±1.1	1.7±0.9	1.5±0.8	1.00	1.00	1.00	0.89
Ao peak velocity (m/s)	1.4±0.4	1.3±0.3	1.3±0.5	0.81	1.00	0.72	0.38
Mitral regurgitation							
MR volume (ml)	37±19	13±8	4±3	**<0.001**	0.62	**<0.001**	**<0.001**
MR fraction (%)	32±14	15±10	5±4	**0.002**	0.20	**<0.001**	**<0.001**
MR improved	10(56)	9(100)	10(100)	n/a	n/a	n/a	**0.005**

Data as mean±SD. ANOVA with Bonferroni correction was used to compare continuous data between groups. LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVSV, left ventricular stroke volume; LVEF, left ventricular ejection fraction; LV, left ventricle; LA, left atrial; Ao, aortic; RF, regurgitant fraction; PG, pressure gradient; MR, mitral regurgitation.

4.4.6 Changes in left ventricular parameters

At 6 months, both surgical groups exhibited a greater reduction in LV end-diastolic volume when compared to the controls (Table 3.6). The indexed LVEDV decreased significantly from 129±33ml to 99±37ml, p<0.001 in the repair group, from 118±24ml to 90±26ml, p<0.001 in the replacement group and remained unchanged in the control group 115±25ml to 113±25ml, p=0.53. The absolute reduction in indexed LV end-diastolic volume was however not significantly different between the repair and replacement groups (-30±15ml vs -29±19ml, repair vs replacement, p=1.00). There was no significant change in the LV end-systolic volume between the groups, and despite a downward trend of LV mass in the surgical groups, this did not reach statistical significance (Table 3.6).

LV stroke volume in both the repair and replacement groups was significantly lower than at baseline, leading in an overall reduced cardiac output. Similarly, there was a decline in the global postoperative LV ejection fraction in those who had surgery (control: 59±5% to 58±6%, p=0.92 vs repair: 54±7% to 45±8% p=0.001 vs replacement 55±7% to 49±9%, p=0.03). The degree of reduction in LV ejection fraction did not differ between the repair and replacement group (-9±6% vs -6±8%, repair vs replacement; p=1.00).

4.4.7 Changes in left atrial parameters

In both types of MV surgery, LA volumes decreased significantly (repair: 92±22ml/m^2 to 50±23ml/m^2, p<0.001 vs replacement: 98±32 ml/m^2 to 62±18 ml/m^2, p<0.001). No significant differences were detected in the degree of indexed LA volume reduction between the surgical groups (-42±26ml/m^2 vs -36±23ml/m^2, repair vs replacement; p= 1.00).

4.4.8 Changes in aortic flow parameters

The MV repair group experienced significant reduction in aortic regurgitation, which was not seen in those undergoing MV replacement (Table 3.7). Although there was an improvement in aortic forward flow postoperatively, (0.8±15ml vs 5.5±11ml, repair vs replacement, p=1.00) this was not statistically different between the groups.

4.4.9 Changes in MR severity

Postoperatively, both the surgical groups sustained a significant reduction in their MR volume (repair: 60±13ml to 13±8ml p<0.001 vs replacement: 50±25ml to 4±3ml p<0.001) and MR fraction (repair: 47±9% to 15±10%, p<0.001 vs replacement: 41±13% to 5±4%, p<0.001) (Table 3.7). The 'replacement' group had a greater degree of reduction in MR fraction when compared to the 'repair' groups although the difference was not statistically significant (-36±12ml vs -32±11ml, repair vs replacement, p=1.00). From the total study population, MR significantly improved in 100% (n=19) of patients following MV surgery (repair or replacement) and worsened in 8/18 patients (44%) patients in the control group.

Table 4.6 Changes in CMR characteristics of patients in 'Controls', 'Repair' and 'Replacement' groups during 6 months follow-up scan

Cardiovascular variables Δ Absolute change	Controls (n=18)	Repair (n=9)	Replace (n=10)	P value (Controls vs Repair)	P value (Repair vs Replace)	P value (Controls vs Replace)	P value ANOVA btwn groups
ΔLV Mass (g)	-1±7	-11±16	-7±11	0.15	1.00	0.53	0.11
ΔLV Mass index (g/m²)	-0.5±4	-5±8	-4±6	0.19	1.00	0.51	0.13
ΔLVEDV (ml)	-4±29	-57±26	-52±34	**<0.001**	1.00	**0.001**	**<0.001**
ΔLVEDV (indexed), ml/m²	-2±16	-30±15	-29±19	**0.001**	1.00	**0.001**	**<0.001**
ΔLVESV (ml)	0.9±13	-7±24	-12±27	0.95	1.00	0.39	0.28
ΔLVESV (indexed), ml/m²	0.6±7	-4±12	-7±14	1.00	1.00	0.28	0.22
ΔLVSV (ml)	0.0±16	-49±17	-41±28	**<0.001**	1.00	**<0.001**	**<0.001**
ΔLVSV (indexed), ml/m²	0.1±8	-26±11	-22±14	**<0.001**	1.00	**<0.001**	**<0.001**
ΔLVEF (%)	-0.1±5	-9±6	-6±8	**0.003**	1.00	**0.05**	**0.002**
ΔLA volume (ml)	5±37	-80±48	-67±38	**<0.001**	1.00	**<0.001**	**<0.001**
ΔLA volume index (ml/m²)	3±20	-42±26	-36±23	**<0.001**	1.00	**<0.001**	**<0.001**
Aortic Flow							
ΔAo forward flow (ml)	1.4±12	0.8±15	5.5±11	1.00	1.00	1.00	0.67
Mitral regurgitation							
ΔMR volume (ml)	-1.5±12	-48±13	-46±23	**<0.001**	1.00	**<0.001**	**<0.001**
ΔMR fraction (%)	-1.8±7	-32±11	-36±12	**<0.001**	1.00	**<0.001**	**<0.001**

Data as mean±SD. ANOVA with Bonferroni correction was used to compare continuous data between groups. LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVSV, left ventricular stroke volume; LVEF, left ventricular ejection fraction; LV, left ventricle; LA, left atrial; Ao, aortic; RF, regurgitant fraction; PG, pressure gradient; MR, mitral regurgitation.

Table 4.7 Baseline and 6 months CMR parameters in the 'Controls', 'Repair' and 'Replacement' groups

Cardiovascular variables	Controls (n=18)			Repair (n=9)			Replace (n=10)			P value ANOVA
	Baseline	6m	p value	Baseline	6 m	p value	Baseline	6 m	p value	
LV Mass (g)	95±20	94±20	0.55	103±25	92±33	0.09	97±33	90±35	0.06	0.11
LV Mass index (g/m^2)	52±10	51±9	0.57	54±13	49±18	0.10	52±14	48±15	0.06	0.13
LVEDV (ml)	209±46	204±46	0.51	244±57	187±66	**<0.001**	220±58	168±60	**<0.001**	**<0.001**
LVEDV (indexed), ml/m^2	115±25	113±25	0.53	129±33	99±37	**<0.001**	118±24	90±26	**<0.001**	**<0.001**
LVESV (ml)	85±23	86±28	0.77	115±38	108±56	0.37	100±32	89±47	0.21	0.28
LVESV (indexed), ml/m^2	46±12	47±15	0.74	61±22	57±31	0.35	54±14	47±22	0.17	0.22
LVSV (ml)	118±21	118±23	1.00	129±24	80±15	**<0.001**	120±34	79±19	**0.001**	**<0.001**
LVSV (indexed), ml/m^2	65±11	65±13	1.00	68±14	42±7	**<0.001**	64±15	43±8	**<0.001**	**<0.001**
LVEF (%)	59±5	58±6	0.92	54±7	45±8	**0.001**	55±7	49±9	**0.03**	**0.002**
LV cardiac output, ml/min	8264± 1517	7932± 1844	0.37	8798± 1410	5801± 1018	**<0.001**	8511± 1845	5517± 1493	**<0.001**	**<0.001**
LV cardiac index, $ml/min/m^2$	4564± 858	4383± 1023	0.36	4642± 823	3069± 643	**<0.001**	4625± 947	2955± 629	**<0.001**	**<0.001**
LA volume (ml)	146±38	152±50	0.55	174±40	94±45	**0.001**	181±60	114±39	**<0.001**	**<0.001**

LA volume index (ml/m^2)	81±22	85±29	0.46	92±22	50±23	**0.001**	98±32	62±18	**<0.001**	**<0.001**
Aortic Flow										
Ao forward flow (ml)	75±20	77±22	0.62	63±20	64±12	0.88	66±21	72±18	0.17	0.67
Ao backward flow (ml)	3.9±4.0	4.1±4.4	0.72	5.3±1.7	3.2±1.7	**0.005**	3.5±2.2	3.4±2.4	0.93	**0.03**
Ao volume (ml)	71±19	73±23	0.59	58±20	61±12	0.57	63±21	67±17	0.25	0.86
Ao RF (%)	5.2±4.1	5.8±5.3	0.37	9.0±3.2	5.2±3.4	**0.01**	5.5±2.8	4.9±3.6	0.70	**0.01**
Ao max PG (mmHg)	8.8±4.8	8.3±5.2	0.53	6.8±1.6	6.3±2.1	0.51	7.1±3.6	7.0±3.3	0.90	0.93
Ao mean PG (mmHg)	1.6±0.8	1.6±1.1	0.97	1.5±0.6	1.7±0.9	0.35	1.4±0.8	1.5±0.8	0.50	0.71
Ao peak velocity (m/s)	1.5±0.4	1.4±0.4	0.41	1.3±0.2	1.3±0.3	0.49	1.3±0.3	1.3±0.5	0.66	0.98
Mitral regurgitation										
MR volume (ml)	39±14	37±19	0.59	60±13	13±8	**<0.001**	50±25	4±3	**<0.001**	**<0.001**
MR fraction (%)	33±12	32±14	0.33	47±9	15±10	**<0.001**	41±13	5±4	**<0.001**	**<0.001**

Data as mean±SD. ANOVA with Bonferroni correction for between group comparisons and paired t-test for within group comparison. LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVSV, left ventricular stroke volume; LVEF, left ventricular ejection fraction; LV, left ventricle; LA, left atrial; Ao, aortic; RF, regurgitant fraction; PG, pressure gradient; MR, mitral regurgitation.

4.5 DISCUSSION

To the best of our knowledge, this is the largest prospective CMR study to date assessing the intermediate-term outcome of MV repair and MV replacement on LV cardiac reverse remodelling. The main findings were 1) MV surgery leads to a positive left atrial and left ventricular reverse remodelling 2) In this small series, MV replacement with chordal preservation appears to have similar postoperative cardiac remodelling as MV repair 3) Decline in global LV ejection fraction is commonly seen following MV surgery 4) MV replacement appears to provide a more effective reduction of MR 5) Residual MR following MV repair did not lead to a less favourable cardiac reverse remodelling in this small patient population.

4.5.1 Baseline findings

In this study, patients with significant MR had both an elevated LV end-diastolic volume and LA volume. The volume overload state of chronic MR results in progressive LV dilatation and an elevated LV filling pressure, reflected in the increase in LA size. The backflow of blood from the LV into the LA during cardiac systole phase is added to the forward stroke volume. As a result of this, the total aortic forward flow and calculated LV ejection fraction are increased in the early phase of MR. Progressive LV dilatation further increases the wall tension according to the Laplace law which results in an increased systolic wall stress and afterload.

Although not statistically significant, CMR identified that those undergoing surgery (MV repair or MV replacement) tended to have larger LVEDV and LA volumes at their baseline scans than those in the control arm. Patients in these two surgical groups also tended to have a higher degree of MR, when quantified by CMR, although again not statistically significant. This is potentially reflecting the accuracy of CMR in discerning subtle difference in the volumetric measurements and MR volume quantitation and its ability to identify patients who are more likely to progress to surgery or have poorer outcomes despite similar

echocardiography profile. Recent studies(121,204) have also indicated that CMR-derived assessment of MR is superior than echo-derived integrative approach in predicting the likelihood for surgery and adverse outcomes. The baseline LV and LA parameters did not differ significantly between patients who underwent MV repair and those who underwent MV replacement. As expected, a relatively lower LV ejection fraction was observed in the surgical groups at baseline than in the control arm, as a drop in LV ejection fraction in severe MR is an indication for surgical intervention.

4.5.2 Cardiac reverse remodelling

Postoperatively at 6 months, both the surgical groups experienced significant positive cardiac reverse remodelling, reflected in the reductions in their LV end-diastolic and LA volume. There were no significant between-group differences in left atrial and left ventricular reverse remodelling. It can therefore be interpreted that MV replacement was associated with similar postoperative remodelling as MV repair. There was also a decline in the global postoperative LV ejection fraction in those who had surgery although the degree of reduction in LV ejection fraction, again, did not differ between the repair and replacement group. These findings are consistent with several echocardiographic studies (68,194,207) and 1 small CMR-based study (n=6 in replacement arm)(208) confirming that MV surgery leads to a significant reduction in LVEF.

Postoperative LV ejection fraction is determined by contractility, preload and after-load. Following MV surgery, the elimination of the low impedance pathway into the LA increases the after-load and at the same time reduces the preload. The elimination of the regurgitant volume leads to a reduction in overall LV volume. As a result of correction of the volume overload state, there is a progressive decline in the LV cavity size (68,194). The overall reduction in LVEF when compared with its baseline is an expected finding due to the reduction of both LV cavity size and the LV stroke volume (as the LV no longer off-load the MR volume into the LA, which previously contributes to its apparent good LVEF). Additionally, this may be a reflection of the increase in afterload afforded by MV intervention. Studies have also shown that MV surgery often leads to an initial

decline in the LV ejection fraction with partial recovery at 12months(209). The adaptation of LV to this change is believed to be dependent on the continuity between the mitral annulus and the papillary muscles (annulo-ventricular continuity) (210). The loss of annulo-ventricular continuity is thought to lead to progressive LV dilatation with eventual decline of LV function(45,210).

Only a small change in LV end-systolic volume (a reflection of LV contractility) was observed following MV surgery. A possible explanation is that none of the patients in the tested population had EF <40% (significant LV impairment), and perhaps their contractility state was not sufficiently impaired for any improvement to be evident. Despite a downward trend in the degree of LV mass in the surgical groups, this was not statistically significant. Due to the nature of remodelling, LV hypertrophy was not a predominant feature of cardiac decompensation in MR and the degree of reverse remodelling in this aspect may, again, not be apparent.

Post-operatively, both surgical groups sustained a significant reduction in MR severity (volume and fraction). MV replacement was however a more robust technique in the correction of MR when compared to the repair group. The higher degree of residual MR in the repair group however did not result in less favourable cardiac reverse remodelling when compared to the replacement group. The lack of durability in correction of MR in the repair group is however disconcerting, given its reported association with further progression and long-term negative outcomes(201,202).

Cardiac reverse remodelling in response to mitral valve repair and replacement has not been extensively described. The general consensus is that mitral valve repair is associated with a more favourable reverse remodelling response than replacement, due to preservation of its chordal (subvalvular) apparatus (182,187,211). Preservation of the subvalvular apparatus maintains LV geometry and allows a reduction in LV radius, and leads to a reduction in wall stress (LV afterload), according to the Laplace equation(209,212). Conversely, end-systolic wall stress can increase after MV replacement without chordal preservation due to the loss of chordal support(188). Fixation of the mitral annulus with a rigid

prosthesis during MV replacement can also interfere with the distension and contraction of the basal myocardial wall. MV replacement with chordal preservation in this new era however has had a positive effect on LV geometry and function, and has been shown to reduce peri-operative mortality and improve long-term survival(45,187,211). A chordal preservation technique helps to retain the tethering effect of the chordal apparatus, and therefore moderating the increase in systolic wall stress that occurs after relief of MR. Although the MV replacement in our study uses the 'partial chordal preservation' technique, there has been data suggesting that no statistically significant differences exists between the 'partial' and 'total' chordal preservation technique(213).

4.5.3 Strengths of methodology

A key strength to this prospective, longitudinal, observational study was the use of CMR to reliably assess ventricular volumes and quantitate MR volume with low intra- and inter-observer variabilities, irrespective of MR jet geometry (114,115). Previous studies in MV surgery have frequently used transthoracic echocardiography for MR assessment, which has limited reproducibility and relies on mathematical assumptions of LV geometry and cavity size, which may not apply in the remodelled ventricle. Furthermore, only a small proportion of patients (approx. 20%) with degenerative valve disease had a combination of holosystolic central and single jet(204) making it challenging for accurate Doppler measurements to be performed. Echocardiographic evaluation of MR severity also requires integration of various qualitative and quantitative measurements (173), which may explain the discrepancies in findings amongst previous studies (159,165–168). Although limited by the small sample size, our study enables a deeper understanding of cardiac reverse remodelling occurring after MV repair and MV replacement, by means of a more precise and reliable imaging technique as CMR. The numbers required to elicit an observable difference are usually much smaller, and the imaging is not reliant on echocardiographic windows or hampered by increased body habitus. The addition of a comparative control arm in our study also adds strength to the study.

Patients undergoing MV repair and MV replacement commonly exhibit different characteristics at baseline, as evident in other retrospective studies. Due to the selected population who are able to undergo the study protocol and the exclusion of some patients from the final analysis (as detailed in methodology), we have a matched group of patients. Although not completely representing 'real-world' practice, where patients undergoing MV replacements are often older with additional comorbidities, this matched-population enabled comparisons between groups to be made. The 6-month follow-up time-frame was justified as the majority of LV reverse remodelling occurs within 6 months following surgery, with less important but ongoing remodelling occurring thereafter(194,208). The presence of coronary artery disease introduces complex confounding of results, complicating analysis(214). In order to attain a more homogenous group of patients and to minimize confounding factors of LV remodelling, we have excluded those with concomitant CABG, tricuspid valve intervention and pacemaker from the final analysis.

In this study protocol, a free-breathing pulse sequence was utilised if patients were not able to breath-hold for a prolonged phase-contrast flow imaging scan. We believe this is unlikely to affect the accuracy of the flow data as previous work have demonstrated that the choice of pulse sequence (free breathing versus breath hold) did not significantly affect the quantitative results(215). Furthermore, flow measurements through the aortic valve from 2 acquisitions were averaged to ensure accuracy of aortic flow measurements in light of the beat-to-beat stroke volume variation in patients with AF.

4.5.4 Comparison with available studies

Our findings contradict much of the published literature on this topic, which reports several advantages to mitral valve repair over replacement in terms of cardiac reverse remodelling(34,183,191). We observed no significant differences in cardiac reverse remodelling between MV repair and MV replacement. Evidence in this field has been largely conflicting. Patients in previous studies (35,36,189,216) exhibit different clinical characteristics pertinent to long term outcomes at baseline (replacement being higher in surgical risk), raising

questions of unadjusted comparisons of outcomes after surgery. Available large data supporting repair over replacement are also retrospective and have used propensity match groups in available registries to reduce selection bias in those non-randomised studies(34,217). Nevertheless, the amount of statistical modelling employed tempered the robustness of these studies. Due to the nature of the registries dating a while back, it is also not possible to ensure that chordal preservation techniques were employed in all MV replacement strategies. Furthermore, a number of studies have also included patients undergoing concomitant CABG(34,42,217) and concomitant tricuspid valve repairs (186), both confounding factors which could influence reverse remodelling outcomes.

A large prospective multicentre international registry study by Lazam et al(217) found that MV repair was associated with lower operative mortality, better long-term survival and fewer valve-related complications compared with MV replacement. This study however only looked at those degenerative MR with a flail leaflet making it difficult for the result to be generalised to all degenerative MV conditions (where posterior or anterior leaflet prolapse are much more common). Furthermore, the study recruitment was between 1980–2005 (spanning over 20 years), in the early days of chordal-sparing techniques. In the current era, surgical risk has decreased markedly and preservation techniques during MV replacement and therefore protective factor of LV geometry and function, have markedly improved(194).

Contrary to these studies, a recent echocardiographic study (n=72) by Senechal et al (194) found that MV replacement with sub-valvular preservation was associated with similar postoperative remodelling as MV repair for organic MR. A large propensity-matched study (n=3286) by Gillinov et al (186) also demonstrated that long-term survival was similar between the repair and replacement strategy when those using valve replacement with chordal preservation were included (organic MR). This notion was also supported by some other studies(41). There are no randomized trials comparing outcomes after MV repair and replacement respectively in the context of degenerative disease. In the ischaemic MR population setting however, a recent randomised

trial by Goldstein et al (42) (using echocardiography) comparing MV repair versus replacement demonstrated more residual MR and hospitalisations in those undergoing repair, with no difference in survival or LV reverse remodelling between the two groups (2 year outcome). The replacement group also tended to have a better improvement in their quality of life in this study. This was supported by another randomized controlled trial by Acker et al (197) demonstrating that there was no significant between-group difference in LV reverse remodelling or mortality outcomes at 12 months. Although these trials only investigated the ischaemic MR population, it has certainly highlighted the need to clarify the evidence behind MV repair versus replacement, especially in this modern era of newer replacement techniques of chordal-preservation. The only prospective study using CMR to compare LV reverse remodelling between repair and replacement (with chordal preservation) for organic MR again did not demonstrate a difference between the two surgical techniques(208). The study was however criticized for its small numbers (n=6 patients in the MV replacement arm).

Unlike other studies (186,217), our study population was matched in terms of age, gender, BMI, surgical risk scores, co-morbidities and valve severity. The typical study population undergoing MV replacement in other studies were often older, more symptomatic and are more likely to have left ventricular dysfunction. Interestingly, despite being a CMR–based study (usually precluding patients who couldn't lie flat) , our study population had a higher proportion of patients with NHYA functional Class III pre-operatively than others (approx. 50% vs 25%)(186). Similar to other studies, majority of the patients in the repair group had a higher prevalence of posterior MV prolapse(186) and that those undergoing replacement had more advanced symptoms with 50% showing NHYA functional Class III versus 33% of patients who underwent repair.

4.5.5 Impact on clinical practice

In this small patient series, MV replacement with chordal preservation appeared to have a similar cardiac reverse remodelling benefits when compared to MV repair. A larger sample size of this study is required to assess if MV replacement

may be an acceptable option in those with more complex mitral valve disease which is possible but difficult to repair.

4.6 LIMITATIONS

Although the work is on-going, the small sample size, single-centre, and observational nature of the study design limits the strength of our conclusions. The exclusion of patients with pacemakers, severe AR and concomitant CABG or tricuspid valve intervention in the final analysis raises the potential for selection bias. These exclusions were however felt to be necessary in order to minimize the number of confounding factors when evaluating cardiac reverse remodelling.

All patients included in this study presented with degenerative MR and were of NHYA Class I-III. The findings can therefore neither be applied to patients with other organic MR aetiologies, such as rheumatic valve disease or endocarditis nor can the results be extrapolated to significantly symptomatic patients with NHYA Class IV. Patients with pulmonary congestion or unstable haemodynamics were excluded, and these data can only be extended to stable ambulatory patients. Hence, this may introduce selection bias by excluding more elderly, frail patients.

Because we excluded patients with contraindications to CMR and specific medical conditions, our study population is again highly selected and so our conclusions cannot be extrapolated to all patients with severe MR. Our middle-aged patient population also meant that the findings cannot be generalized to the typical young patients undergoing MV repair. Additionally, our study had a high proportion of patients with AF (35%), an arrhythmia which could make the quantification of flow challenging. In order to overcome this, we performed two acquisition of aortic phase contrast imaging in these patients in order to obtain an averaged, more accurate reading of aortic flow.

Based on the published data by Bellenger et al(218), the group size required to detect a 10ml change in LVEDV is 12 patients, 10 patients to detect a 10ml change in LVESV, 15 to detect a 3% change in LVEF and 9 to detect a 10g change in LV mass. It is therefore possible that our study is currently under-powered to detect a difference between the two surgical groups. It is encouraging however that the CMR parameters in the surgical groups were clearly distinguishable from those in the control arm. When performing CMR measurements in patients with heart valve replacement, there is also a potential for flow and volume miscalculation due to prosthesis-related distortions of the magnetic field (180). Careful planning to avoid metallic artefacts during PC imaging and consistency in contouring LV volumes at the base of the ventricles when a prosthesis is present increased accuracy in measurements.

Manual tracing of endocardial borders at the base of the heart to derive LV volumes can also be challenging in the presence of a prosthetic material in the mitral annulus position. We adhered to the conventional method(219) where ventricular slices were considered to be within the left ventricle if the blood volume was surrounded by 50% of more of the ventricular myocardium. In the presence of a MV prosthesis, the basal slice could potentially be omitted from analysis which results in a smaller post-operative LV volume. This can therefore lead to an overestimation of the degree of reverse remodelling offered by surgical intervention. In addition, omission of basal slices due to artefacts from MV prosthesis could result in an overall smaller LV stroke volume, and can therefore underestimate the degree of post-operative residual MR. Blinding the analysis was also not possible as prosthesis would be visible on the CMR images in those who underwent surgical intervention.

In addition, inherent limitations of PC imaging (including phase offset, suboptimal selection of velocity-encoding gradients during acquisition, and reliance on image plane selection) can interfere with optimal quantification of aortic flow. Measurement of aortic flow at the sino-tubular junction (instead of at the level of the valve) might also underestimate the aortic flow by 10% to 15%(220), and thus cause modest overestimation of the MR. However, quantitation of MR severity by

CMR is generally associated with high accuracy and reproducibility(114,221). There is also the possibility that a 6-month follow-up scan may have been too early to identify any difference in reverse remodelling between the groups.

4.7 CONCLUSION

MV surgery leads to positive left atrial and left ventricular reverse remodelling. A decline in global LV ejection fraction is a common post-operative finding. In this small series, MV replacement with chordal preservation techniques showed similar cardiac reverse remodelling benefits to MV repair. Although residual MR is often seen following repair, this did not appear to lead to a less favourable cardiac reverse remodelling in this small patient population.

Chapter 5 Feasibility and reproducibility of a CMR free-breathing, multi-shot, navigated cine image acquisition technique for ventricular volume quantification during continuous exercise

5.1 ABSTRACT

Background

CMR image acquisition techniques during exercise typically require either transient cessation of exercise or complex post-processing analysis of real-time images, potentially compromising their clinical utility. This study evaluated the feasibility and reproducibility of a free-breathing, multi-shot, navigated cine image acquisition method for biventricular physiological assessment during continuous physical exercise.

Methods

10 healthy volunteers underwent supine cycle ergometer (Lode) exercise CMR on two separate occasions using a free-breathing, multi-shot, navigated, balanced steady-state free precession cine pulse sequence. Individual target heart rates (HR) for both moderate and high-intensity exercise were prescribed based on a prior supine cardiopulmonary exercise test in each subject. The scan protocol included a short axis ventricular volume stack and a 4-chamber cine. Images were acquired at 3-stages, baseline and during steady-state moderate and high-intensity exercise (55% and 75% maximal HR, respectively). Intra-and inter-observer variability and inter-scan reproducibility were derived.

Results

End-diastolic volume (EDV) of both LV and RV decreased during moderate and high-intensity exercise, although the reduction in indexed RVEDV was only observed during maximal exercise. Whilst a reduction in end-systolic volumes (ESV) was seen in both ventricles, the decrease was more evident during high-intensity exercise in the indexed LVESV. Ejection fractions (EF) for both ventricles were significantly higher during high-intensity exercise when compared to their respective baseline (LVEF 68±3% vs 58±5%; p=0.001 and RVEF 66±4% vs 58±7%; p=0.02).

Intra-observer reproducibility of LV parameters was excellent at all three stages. Although measurements of RVESV were more variable during exercise, the reproducibility of both RV ejection fraction and RV cardiac indexes was however excellent (CV<10%). Similarly, inter-observer reproducibility of LV volumes, EF and cardiac indexes was excellent (CV≤10%). Inter-scan LV and RV ejection fraction were highly reproducible at all 3 stages, although inter-scan reproducibility of indexed RVESV was only moderate.

Conclusion

This exercise CMR protocol using a novel application of a free-breathing, multi-shot, navigated cine imaging method allows simultaneous assessment of left and right ventricular response during *continuous* exercise. Intra- and inter-observer reproducibility were excellent. Inter-scan LV and RV ejection fraction were also highly reproducible.

5.2 BACKGROUND

Physiological exercise testing can be used to detect underlying cardiovascular abnormalities which are not apparent at rest. Whilst exercise-stress echocardiography and nuclear scintigraphy are widely available, their limitations include poor acoustic windows(222), motion artefacts(223) and radiation exposure(224). CMR imaging at rest is highly accurate and reproducible, and should be considered in patients with suboptimal echocardiographic imaging(122,206). Although physical exercise is the preferred method of cardiovascular stress testing, it presents significant challenges for use with CMR. The early evolution of exercise CMR (exCMR) focused on improving the MRI-compatibility of exercise treadmill equipment from being placed external to the MRI room(225), to being in close proximity to the MRI scanner(226–228), to a fully MRI compatible treadmill placed adjacent to the MRI system(227,229–231). These protocols are however limited by the time delay needed to transfer the patient from the treadmill onto the scanner. Any time delay in completing stress imaging is critical, since exercise-induced functional abnormalities may begin to disappear almost immediately after exercise cessation(232–234). The transfer could also be unsafe for de-conditioned cardiac patients, particularly after completing maximal exercise stress.

The development of a MRI-compatible cycle ergometer allows patients to exercise on a supine bike whilst inside the bore of the magnet(235). Imaging during continuous exercise eliminates the time lapse between exercise and imaging and may allow a more accurate assessment of changes in cardiac physiology during exertion. Excessive motion during exercise however poses a challenge in image acquisition. As a result, investigators have resorted to acquire images following transient cessation of exercise(236), during breath-holds(225,236,237) or using ungated real-time cine imaging(238). Reconstruction of a short axis stack for volumetric analysis from ungated real-time imaging, however, involves complex post-processing analysis in addition to a requirement for bespoke in-house software, that is not widely commercially available(238).

The objective of this study was to assess the feasibility and reproducibility of a navigated cine image acquisition method for the assessment of the biventricular physiological response during continuous physical exercise. *Hypothesis:* Exercise CMR protocol using the free-breathing, multi-shot, navigated cine image acquisition for ventricular assessment during continuous physical exercise is feasible and has a good intra- and inter-observer reproducibility.

5.3 METHODS

5.3.1 Study design and population

This study was performed in 2 stages: 1) a pilot phase in which the feasibility of a navigated image acquisition sequence was tested in healthy volunteers; 2) an assessment of reproducibility in which each healthy volunteer underwent a repeat exCMR after a median of 16 weeks. The study was approved by a local ethics committee (Yorkshire & The Humber-Leeds West 12/YH/0551) and complied with the Declaration of Helsinki. All participants provided written informed consent (See Appendix).

5.3.2 Pilot phase and reproducibility

Ten healthy volunteers with no history or symptoms of cardiovascular disease and no contraindications to CMR were recruited. Absolute and relative contraindications to exercise testing were also adhered to according to AHA guidelines(239). This included the presence of acute myocardial infarction, high-risk unstable angina, uncontrolled cardiac arrhythmias, decompensated heart failure, acute pulmonary embolus and physical disability that could preclude safe and adequate test performance. Participants with known left main stem stenosis without revascularisation, major electrolyte abnormalities, significant stenotic valvular heart disease, tachy or bradyarrhythmias, AF with uncontrolled ventricular rate, high-degree atrioventricular node block, hypertrophic cardiomyopathy or uncontrolled hypertension were also excluded. The maximum

HR achieved with supine cycling is often lower compared to upright cycling (236,238) or upright exercise treadmill (240–242). The AHA guidelines(239) recommended that both diagnostic and prognostic evaluations might be better served by testing protocols tailored to each patient's "true" maximum exercise capacity. In order to personalize individual target HRs based on the maximal HR achieved on a supine exercise test, all healthy volunteers underwent a supine cardiopulmonary exercise test (CPET) prior to undertaking exCMR on a supine cycle ergometer.

CMR was performed on a 1.5 Tesla MRI system (Ingenia, Philips Healthcare, Best, Netherlands) equipped with a 28-channel coil and free-breathing images were acquired during continuous exercise. Exercise intensity was individualised to the HR corresponding to 55% and 75% of the maximal HR attained on their supine CPET (defined as 'moderate' and 'high'-intensity exercise, respectively). After a median time of 16 weeks, exCMR was repeated using an identical scanner and protocol. The long gap between scan and re-scan was a result of an unforeseen logistical issue when the MRI compatible ergometer was unexpectedly magnetised and had to be sent back to its manufacturer in Netherlands to be de-magnetised.

5.3.3 Cardiopulmonary exercise testing

All healthy volunteers underwent CPET on a supine cycle ergometer (Lode BV, Groningen, The Netherlands). The crank length on the cycle ergometer was adjusted to replicate the setup of the in-scanner MRI ergometer. CPET was conducted as a ramp incremental test (15 W/min) to volitional fatigue. Breath-by-breath analysis of the volume and concentration of expired gases was achieved with the use of an automated system (Medgraphics Ultima, Minnesota, USA) with a paramagnetic oxygen analyzer and infrared carbon dioxide analyzer after calibration against a standardized gas solution. HR was continuously monitored via an attached 12-lead electrocardiogram (ECG). The main outcome measures were maximal HR and maximal power output in Watts. ExCMR was performed after a median of 8 days (IQR 2-13).

5.3.4 Exercise CMR protocol and image acquisition

Exercise whilst in the bore of the magnet was conducted on a supine MRI-compatible cycle ergometer (Lode BV, Groningen, The Netherlands). Optimal participant preparation included instructions on consistent thoracic breathing, use of handrail to ensure trunk stability, skin preparation to maximize interface between electrode and skin, and securing vector ECG connections onto the anterior chest wall with tape to ensure quality recording of ECG. A BP cuff was placed on the left arm. Both the surface coil and torso pad were then firmly secured onto the participants with elastic Velcro® straps. The MRI table was advanced whilst participants performed a short bout of unloaded exercise to ensure that their knees did not contact the external casing of the scanner during pedalling. *Figure 5.1* demonstrates the exam room layout for exercise CMR whilst *Figure 5.2* depicts the preparation steps prior to exercise CMR.

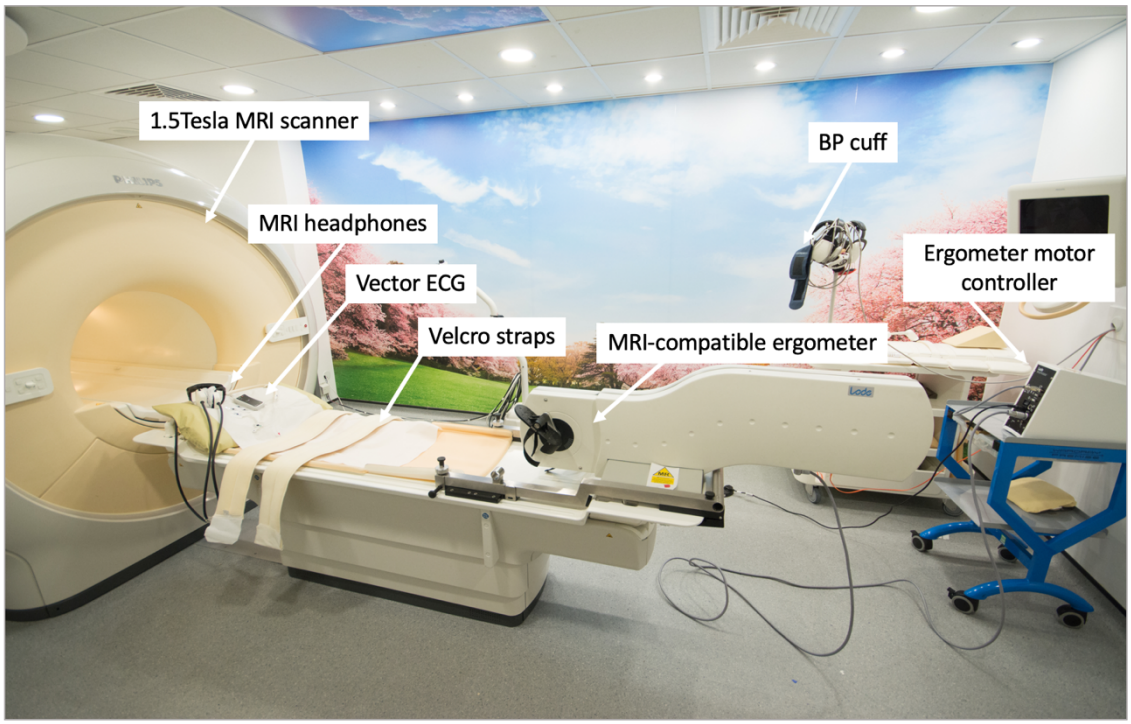

Figure 5.1 Exam room layout for exercise CMR

The MRI-compatible supine ergometer, MRI headphones, vector ECG box, elastic Velcro® straps, ergometer motor controller and BP unit are all within the MRI room. The motor controller adjusts electronic resistance on the ergometer. Magnetic resonance imaging, MRI; electrocardiogram, ECG; blood pressure, BP.

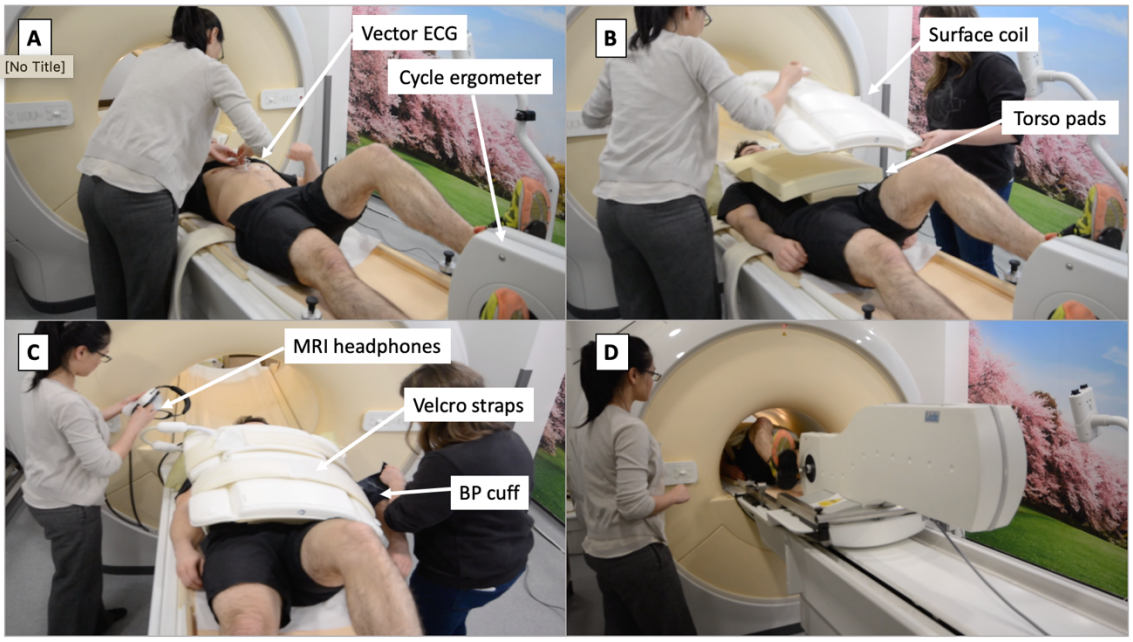

Figure 5.2 Preparation steps for navigated exercise CMR.
A- vector ECG connections were firmly secured onto the participants; B- torso pads and surface coil were placed onto the chest wall; C- elastic Velcro® straps were used to firmly secure the torso, torso pads, and surface coil in order to reduce movement artefacts, and both BP cuff and headphones were attached; D- table was advanced into the MRI scanner whilst participants performed a short bout of unloaded exercise. Electrocardiogram, ECG; blood pressure, BP; magnetic resonance imaging, MRI.

Free-breathing images were acquired at 3-stages, at rest and then during steady-state exercise at two intensities: 'moderate' and 'high'-intensity, as defined above. Exercise began with a 2min warm-up at a power output of 0W (unloaded). Work rate was incrementally increased by 10-20W until the target HR for 'moderate'-intensity exercise was achieved. Verbal feedback was constantly given to participants and cycling cadence was maintained between 60-70rpm. Following a rest of 2 minutes, a second bout of exercise was undertaken until the target HR for 'high'-intensity exercise was achieved. Heart rate and rhythm were continuously monitored, and BP was recorded at all stages. Each stage of

exercise was maintained for 5-7mins (2 minutes to achieve steady-state and approximately 3-5mins of image acquisition).

Unlike real-time imaging, the images for the entire LV short axis stack were reconstructed over a 3-5 min acquisition period in this navigated imaging sequence. Steady-state exercise is regarded as the level of exercise that achieves a balance between the energy required by working muscle and the rate of oxygen and delivery for aerobic adenosine triphosphate (ATP) production(243). In this study, there is an assumption that steady-state conditions are met when HR is invariant. HR variation was monitored and recorded every 30 seconds throughout the exercise regime. Example of HR recording can be seen in *Figure 5.3*. Imaging was only performed during steady-state conditions, when HR was maintained at reasonably constant levels. Standard criteria for termination prior to achieving target HR were observed including: participant's request, significant arrhythmias, drop in systolic BP >10mmHg or any ST-segment elevation.

The scan protocol included standard long axis views (vertical, horizontal long axis) and a short axis ventricular volume stack. Cine imaging was performed using a free-breathing, multi-shot, respiratory-navigated, balanced steady-state free precession pulse sequence. Respiratory echo-based navigator was placed on the right hemi-diaphragm with a 5mm gating window and continuous gating level drift activated. A cylindrical MR radiofrequency excitation pulse from which a 1-dimensional projection of the lung-liver interface was generated and was used to infer the breathing phase. The 'gate and track' setting used in this study tracked the breathing pattern of the subject throughout the scan and adapted the position of the gating window in maximising the gating efficiency. The linear relationship between the respiratory motion of the right hemi-diaphragm (RHD) and the heart allowed diaphragmatic navigators to track the RHD motion to indirectly correct the respiratory motion of the heart. The RHD position was initially measured to determine its location at end-expiration. Immediately before each acquisition of k-space lines, the RHD position was measured and the accept/reject algorithm was activated. Cartesian sampling was used, and the acquired k-space lines were only accepted for image reconstruction if the RHD position was within the

gating window during end-expiratory phase. Otherwise, those lines were rejected and reacquired until they are all acquired within the gating window. The scan was completed when all k-space lines were acquired within a gating window around an RHD position.

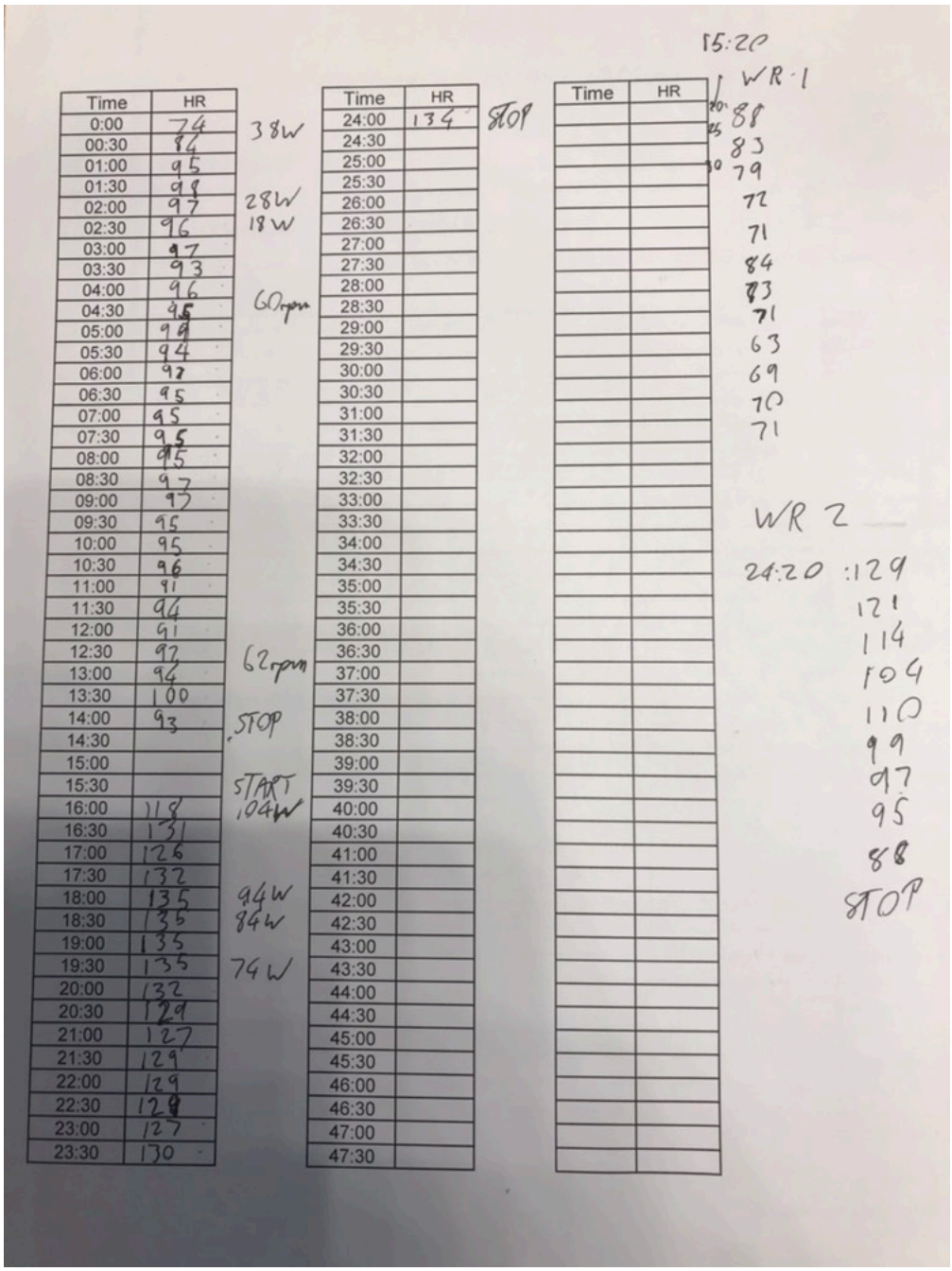

Figure 5.3 Example of heart rate recording during exercise CMR.

Image acquisition was taken for moderate intensity exercise during minute 03:00-09:00; and during minute 20:00-24:00 for high intensity exercise.

Other scan parameters were as follows: typical FOV 320x320mm, TR 2.8msec, TE 1.4msec, flip angle 60°, temporal resolution 33msec, SENSE factor 2, multi-shot TFE factor 11, TFE acquisition duration 30.4ms, phase percentage 50%, slice thickness 10mm, 0mm gap, 30 phases, in-plane spatial resolution 2.4×2.4mm, matrix 132x106. Due to the absence of ethical approval for invasive testing, this study did not look into assessing the accuracy of this imaging method against invasive standards (direct Fick method) in deriving cardiac output.

5.3.5 CMR analysis

CMR analysis was performed by two independent operators (PC, LB). Left and right ventricular volumes, ejection fractions, stroke volume and cardiac output were calculated based on the general methodology described in Chapter 2. Extra care was taken to identify the LV end-diastole and end-systole phase with simultaneous reference to the long axis images of the ventricles to identify the position of the atrioventricular plane.

5.3.6 Statistical analysis

General statistical analysis were as described in Chapter 2. Repeated measures ANOVA with Bonferroni post-test analysis was used to compare data between rest and different stages of exercise. Intra-observer variability was defined as the amount of variation one operator experiences when CMR measurements were repeated in the same dataset, whereas inter-observer variability was the amount of variation between results obtained by two independent operators. Intra- and inter-observer reproducibility was assessed by the Coefficient of Variation (CV) test, the standard deviation of differences between observations divided by the mean. $P<0.05$ was considered statistically significant.

5.4 RESULTS

5.4.1 Healthy volunteers and baseline CMR data

All 10 healthy volunteers (7 men, age 25±2 years, BMI 23.1±2.2 kg/m^2) completed the full study protocol. HR increased substantially during exercise (68±12bpm vs 94±13bpm vs 131±11bpm, baseline vs moderate vs high; all $p<0.001$). Systolic BP was significantly higher during high-intensity exercise than at baseline (130±12mmHg vs 120±10mmHg; $p=0.03$), whilst diastolic BP remained unchanged (70±14mmHg vs 70±8mmHg; $p=1.00$). Mean work rate for moderate and high-intensity exercise was 25±19W and 87±23W, respectively. CMR data for all subjects are described in Table 4.1.

5.4.2 Left and right ventricular parameters during exercise

The changes in ventricular volumes during exercise are plotted in Figure 4.1. End-diastolic volume of the LV decreased significantly during moderate and high-intensity exercise. In contrast, RVEDV remained unchanged from baseline during moderate-intensity exercise and significantly decreased during high-intensity exercise ($p=0.02$). LV end-systolic volume decreased from moderate to high-intensity exercise ($p=0.02$). LVESV during moderate exercise, however, was not significantly different from rest. RV end-systolic volume significantly decreased during high-intensity exercise compared to baseline. Both LV and RV stroke volumes remained unchanged. Ejection fraction for both ventricles were significantly higher during high-intensity exercise when compared to their respective baseline values (LVEF 68±3% vs 58±5%; $p=0.001$ and RVEF 66±4% vs 58±7%; $p=0.02$). During exercise, LV and RV cardiac indexes also increased significantly (Figure 4.2).

Table 5.1 Volumetric data at baseline, and during moderate and high-intensity exercise in healthy volunteers

Cardiovascular variables	Baseline	Moderate Intensity	High Intensity	P value (Baseline vs Moderate)	P value (Moderate vs High)	P value (Baseline vs High)
LVEDV (ml)	182±28	175±27	159±22	0.003	0.010	0.001
LVEDV (indexed), ml/m^2	97±11	93±10	85±7	0.002	0.012	0.001
LVESV (ml)	77±18	68±19	52±9	0.269	0.022	0.001
LVESV (indexed), ml/m^2	41±7	36±9	28±3	0.252	0.019	0.001
LVSV (ml)	105±14	107±21	107±15	1.000	1.000	1.000
LVSV (indexed), ml/m^2	57±6	57±10	57±5	1.000	1.000	1.000
LVEF (%)	58±5	61±8	68±3	0.912	0.109	0.001
LV cardiac output, ml/min	7087± 1392	10188± 2902	14041± 2454	0.004	0.005	<0.001
LV cardiac index, ml/min/m^2	3805± 721	5456± 1448	7503± 1055	0.003	0.003	<0.001
RVEDV (ml)	178±30	171±182	152±25	0.257	0.022	0.011
RVEDV (indexed), ml/m^2	95±11	92±8	81±7	0.231	0.020	0.009
RVESV (ml)	76±21	66±18	52±12	0.119	0.134	0.017
RVESV (indexed), ml/m^2	40±10	35±8	28±5	0.124	0.129	0.011

RVSV (ml)	102±17	105±14	101±16	1.000	1.000	1.000
RVSV (indexed), ml/m^2	51±9	56±5	54±5	0.270	1.000	0.872
RVEF (%)	58±7	62±7	66±4	0.365	0.463	0.017
RV cardiac output, ml/min	6869± 1752	9957± 2327	13119± 2196	0.002	0.009	<0.001
RV cardiac index, ml/min/m^2	3685± 907	5333± 1133	6991± 704	0.002	0.007	<0.001

Data as mean±SD. ANOVA with Bonferroni correction was used to compare continuous data between groups. LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVSV, left ventricular stroke volume; LVEF, left ventricular ejection fraction; LV, left ventricle; RVEDV, right ventricular end-diastolic volume; RVESV, right ventricular end-systolic volume; RVSV, right ventricular stroke volume; RVEF, right ventricular ejection fraction; RV, right ventricle

5.4.3 Intra- and inter-observer reproducibility

Intra-observer reproducibility of LV volumes, LV ejection fraction and LV cardiac index was excellent at all three stages, evidenced by CV ≤10% (Table 4.2). During exercise, the measurements of RVESV were more variable (CV 11-20%). The reproducibility of RV end-diastolic volume, RV ejection fraction, and RV cardiac index was however excellent (CV <10%).

Inter-observer reproducibility of LV volumes, LV ejection fraction and LV cardiac index was also excellent at all three stages (CV for LVEDV≤5%; LVESV ≤10%; LVEF <6%; LV cardiac index <8%). With incremental exercise, inter-observer reproducibility was better in the assessment of RVEDV (CV <5%), when compared to RVESV measurements (CV 12-14%). Although measurements of RVESV were more variable during exercise, the reproducibility of RV ejection fraction, RV stroke volume and RV cardiac index was however excellent. During high-intensity exercise, inter-observer LVESV was more reproducible than RVESV (CV 10% vs 14%)

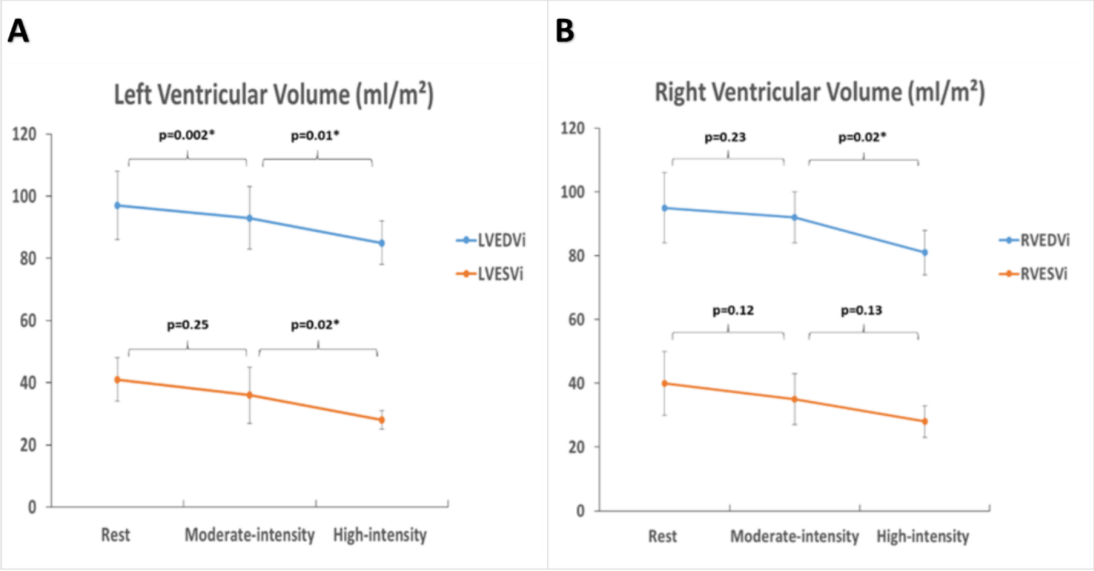

Figure 5.4 Ventricular volumes during exercise in healthy volunteers

Left ventricular (Panel A) and right ventricular (Panel B) end-diastolic and end-systolic volumes during exercise in healthy volunteers. Indexed left ventricular end-diastolic volume, LVEDVi; indexed left ventricular end-systolic volume, LVESVi; indexed right ventricular end-diastolic volume, RVEDVi; indexed right ventricular end-systolic volume, RVESVi

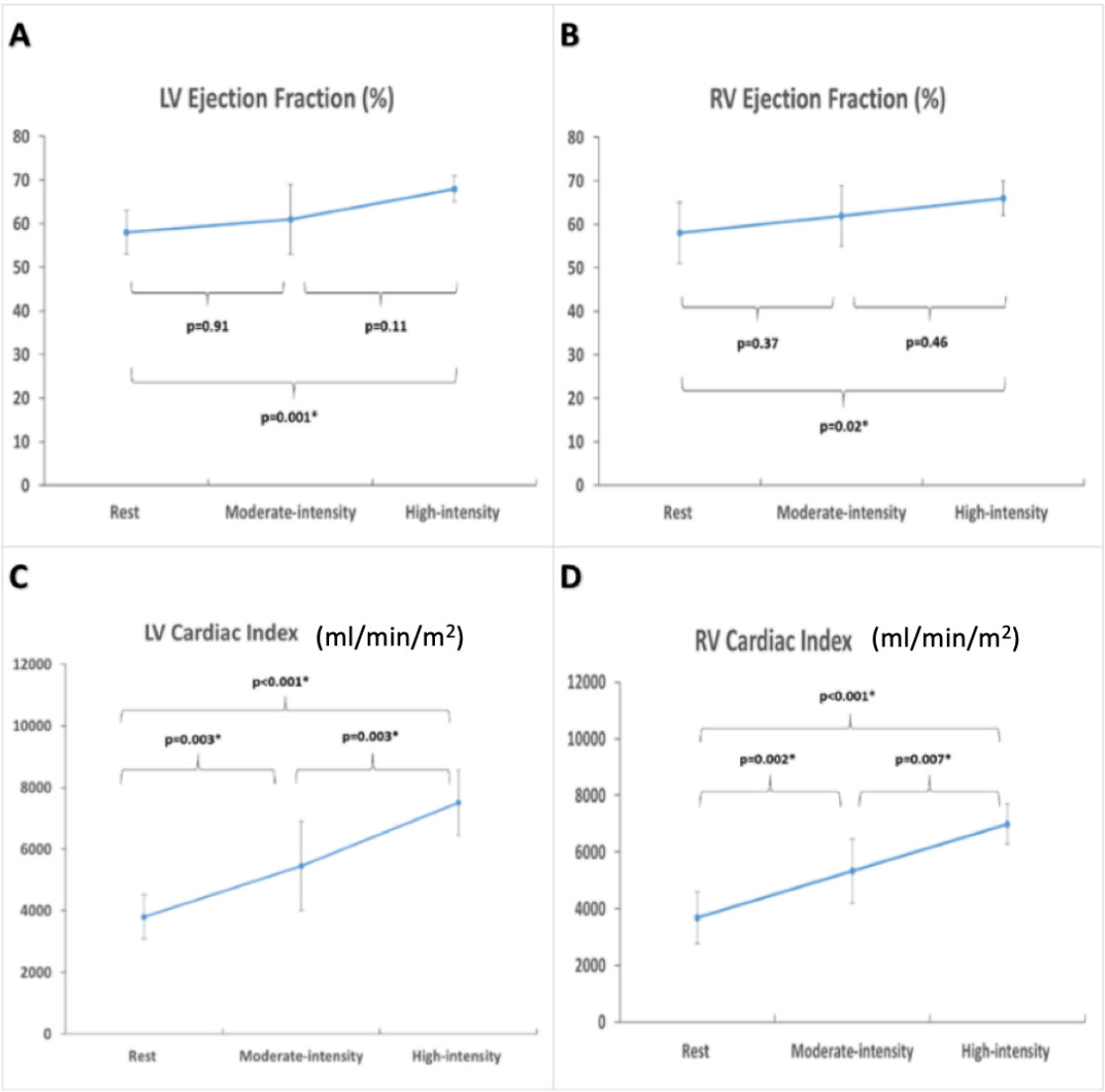

Figure 5.5 Exercise cardiac reserve in healthy volunteers

Left and right ventricular ejection fraction (Panel A and B); left and right ventricular cardiac indexes (Panel C and D) during exercise in healthy volunteers. Data presented in mean (dots) and standard deviation (bars). Asterisks denote statistically significant differences ($p<0.05$).

Table 5.2 Coefficient of Variation for the reproducibility of LV and RV cardiac indices

Stages	Cardiovascular variables	Coefficient of Variation for Reproducibility (%)		
		Intra-Observer	Inter-observer	Inter-scan
REST	LVEDVi	3.3	2.6	7.6
	LVESVi	8.1	7.3	6.8
	LVSVi	4.3	6.4	12.7
	LVEF	4.5	5.4	6.5
	LV CI	4.3	5.3	15.1
	RVEDVi	4.3	4.8	7.1
	RVESVi	9.6	9.8	15.1
	RVSVi	8.5	6.5	11.4
	RVEF	6.8	5.1	10.3
	RV CI	8.5	5.7	17.2
Moderate Intensity (55% max HR)	LVEDVi	3.2	2.7	5.5
	LVESVi	10.0	6.5	11.7
	LVSVi	5.1	5.3	12.5
	LVEF	5.6	3.7	9.2
	LV CI	5.1	5.3	16.0

	RVEDVi	5.5	4.6	8.3
	RVESVi	11.6	12.4	16.1
	RVSVi	6.3	5.8	9.5
	RVEF	5.1	6.0	7.1
	RV CI	6.3	6.0	12.3
High intensity (75% max HR)	**LVEDVi**	6.4	4.8	7.1
	LVESVi	9.8	10.0	11.6
	LVSVi	9.3	7.3	10.1
	LVEF	4.9	5.3	5.8
	LV CI	9.1	7.1	10.1
	RVEDVi	6.6	3.5	12.1
	RVESVi	19.5	13.6	23.5
	RVSVi	8.4	4.9	10.4
	RVEF	7.7	5.5	8.5
	RV CI	8.5	4.8	8.8

Data as %. LVEDVi, indexed left ventricular end-diastolic volume; LVESVi, indexed left ventricular end-systolic volume; LVSVi, indexed left ventricular stroke volume; LVEF, left ventricular ejection fraction; LV CI, left ventricular cardiac index; RVEDVi, indexed right ventricular end-diastolic volume; RVESVi, indexed right ventricular end-systolic volume; RVSVi, indexed right ventricular stroke volume; RVEF, right ventricular ejection fraction; RV CI, right ventricular cardiac index; HR, heart rate

5.4.4 Inter-scan reproducibility

We observed good inter-scan reproducibility for LV end-diastolic and end-systolic volumes during exercise; although only modest reproducibility was seen in the readings of LV cardiac index (CV 10-16%). The RVESV measurements were the least reproducible (CV 11-24%). Inter-scan LV and RV ejection fraction were however highly reproducible (CV<10%) at all 3 stages.

5.5 DISCUSSION

This study demonstrated the 1) feasibility of the free-breathing, multi-shot, navigated cine image acquisition method in the serial assessment of biventricular response to *continuous* exercise; 2) excellent intra- and inter-observer reproducibility, in particular the left ventricular indices.

ExCMR has the potential of providing quantitative cardiac indices; whilst offering a direct link between physical activity, symptoms and stress imaging findings. Additionally, it offers important information such as functional capacity, BP response and developments of arrhythmias. Robust image acquisition techniques are necessary to accommodate free-breathing exercise protocols. It has been well-documented that exercise-induced functional abnormalities dissipate rapidly once exercise stops due to rapidly declining HR (232,233). Current imaging modalities have nevertheless found it challenging to complete imaging before wall motion abnormalities generated under stress conditions begins to diminish immediately following cessation of exercise. Imaging during continuous exercise eliminate the time lapse between exercise and imaging and may allow a more accurate assessment of changes in cardiac physiology during exertion. CMR image acquisition techniques during exercise however typically require transient cessation of exercise or complex post-processing analysis.

5.5.1 Image acquisition techniques

Image acquisition techniques used with the MRI cycle ergometer have either involved a brief period of exercise cessation(236) or required a breath-hold protocol(225,237) in order to reduce excessive motion artefacts and avoid poor ECG signal. Ungated real-time CMR imaging(238,244,245) has been a method that enabled cine images to be acquired during continuous exercise. However, the post-processing analysis of these images requires retrospective synchronization of ECG and respiratory movements, in addition to the need of non-commercially available in-house software(238). The application of other image acquisition techniques such as motion correction(246,247) can be challenging in this setting due to the large amount of through plane motion during exercise. When real-time imaging was applied to the exercise treadmill setting (229), where images were acquired during free-breathing immediately after exercise, it required extensive pre-preparation. This included pre-scanning of the localizing slice, prior patient positioning on the MRI table, and the transfer of patient immediately after exercise to the exact same position which may be challenging in clinical practice.

Navigator-echo-based gating techniques have been practical methods for effective reduction of respiration motion effects, and are well established for coronary CMR imaging(248,249). Navigator gating during free-breathing has also been shown to achieve image quality and scan time equivalent to breath-holding for MR coronary angiography(250). Our feasibility study demonstrated that the application of respiratory-navigated technique in exCMR has the potential to overcome respiratory motion which can be quite significant during strenuous exercise. This technique was feasible in healthy volunteers, and the images acquired were analysable and reproducible. Moreover, this imaging technique allowed serial assessment of cardiac function with incremental exercise and a further advantage is that image analysis can be performed on commercially available software. This protocol therefore has the potential to increase the utility of exCMR as a clinical assessment tool.

The ‘gate and track’ setting used in this study tracked the breathing pattern of the subject throughout the scan and adapted the position of the gating window in maximising the gating efficiency. The linear relationship between the respiratory motion of the right hemi-diaphragm (RHD) and the heart allowed diaphragmatic navigators to track the RHD motion to indirectly correct the respiratory motion of the heart(251). The RHD position was initially measured to determine its location at end-expiration. A small gating window, typically 5–7 mm, was then placed around the end-expiratory position. Immediately before each acquisition of k-space lines, the RHD position was measured and the accept/reject algorithm (248,252) was activated. If the RHD position was within the gating window, the acquired k-space lines were accepted for image reconstruction. Otherwise, those lines were rejected and reacquired until they are all acquired within the gating window (253). The scan was completed when all k-space lines were acquired within a gating window around an RHD position.

5.5.2 Current progress of bi-ventricular assessment with exCMR

Using an ultrafast turbo field echo planar imaging (EPI) gated sequence, Roest et al in 2001 (236) imaged during brief cessation in cycling and breath-hold. At any one point, only 2 short-axis slices within 8 heart beats were acquired and subjects continued cycling prior to the next image acquisition. Multiple brief cessations of exercise and breath holds (up to 5 times) were needed in order to attain a full 10 short-axis slices of LV stacks, thus limiting clinical utility. Lurz et al (244,254) later provided experience of real-time ungated CMR imaging during exercise. They utilized straight leg kicking exercise, which is unconventional compared to a rotating cycling exercise and involves less physical work. La Gerche et al(238) then compared real-time ungated with gated CMR techniques and demonstrated that despite its complex post-processing analysis, ventricular volumes were analysable more frequently with real-time ungated compared with gated CMR (100% vs 47%; $p<0.001$). In our gated CMR study, when combined with ‘respiratory-navigation’, sufficient image quality for analysis was achieved in 100% of the scans. La Gerche et al also observed better interobserver variability for real-time ungated (CV=1.9% and 2.0% for LV and RV stroke volumes, respectively) than gated scans (CV=15.2% and 13.6%; $p<0.01$)(238). Comparing their gated study to ours, the incorporation of ‘respiratory-navigation’ in our gated

study improved the CV for left and right ventricular stroke volumes (CV of 7.3% and 4.9%, during high-intensity exercise, respectively).

In 2017, Le et al (245) combined real-time imaging with ECG-gated sequences to assess exercise cardiac volumes in healthy volunteers and athletes. Image acquisition, however, required suspension of exercise at the end of every stage for free-breathing imaging. The decline in HR following cessation of exercise(234,255) can potentially impair diagnostic accuracy and clinical utility. In contrast, our exCMR protocol permits imaging during *continuous* exercise, eliminating the time lapse between exercise and imaging altogether. In relation to scan parameters, our study had a better temporal resolution (33msec vs 39msec) and a smaller voxel size (2.4x2.4mm vs 3.3x2.3mm) indicating improved spatial resolution.

5.5.3 Exercise protocol

The maximum HR achieved with supine cycling is often lower compared to upright cycling (236,238) or upright exercise treadmill (240–242). The AHA guidelines recommended that both diagnostic and prognostic evaluations might be better served by testing protocols tailored to each patient's "true" maximum exercise capacity(239). We have therefore taken measures to personalize individual target HRs based on the maximal HR achieved on their supine CPET test. 55% and 75% were selected to represent 'moderate' and 'high'-intensity exercise; and this was based upon the limits of the scanner's capability for this pulse sequence (max HR 140). This exCMR protocol included an initial warm-up period, followed by progressive graded exercise with increasing workloads and an adequate time interval in each level. Imaging was only performed during steady-state conditions; when HR, cardiac output, BP, and pulmonary ventilation are maintained at reasonably constant levels (i.e. 2-3 minutes after target HRs were achieved). With cycle ergometer, upper body motion is usually reduced, making it easier to obtain BP measurements and to record the ECG signals.

5.5.4 Cardiovascular responses to exercise in healthy volunteers

During exercise, the cardiovascular system adapts to meet increased oxygen demands of the peripheral muscles(239). Stimulation of the sympathetic system and withdrawal of vagal tone result in increasing heart rate and myocardial contractility, and a decrease in systemic vascular resistance, thus increasing cardiac output(256). Cardiac output is increased by an augmentation in stroke volume (mediated through the Frank-Starling mechanism) and HR(239). However, at moderate- to high-intensity exercise, the continued rise in CO is primarily attributable to an increase in HR, as stroke volume typically reaches a plateau at 50% to 60% of maximal oxygen. Systolic BP rises with increasing dynamic work as a result of increasing CO, whereas diastolic pressure usually remains about the same because of vasodilatation of the vascular bed, consistent with known physiology (239). Physiological responses can however be significantly different, depending on dynamic/static contractions; or aerobic/anaerobic contributions(239).

5.5.5 Volumetric measurements

The effects of left and right ventricular volumes during physical exercise remains controversial. The interactive effects of body posture (i.e. upright, semi-recumbent, recumbent) and types of exercise (i.e. dynamic, static, aerobic, anaerobic) on physiological responses also remain debatable despite extensive study(239). Methodologic limitations due to different imaging modalities may account for the lack of consistency in previous studies. CMR offers important advantages over other methods as the technique is not dependent on geometric assumptions and does not require pharmacological stress agent which has intrinsic effect on the cardiovascular system. Some data are generally consistent with an enhanced contractile state during supine exercise, but the role of the Frank-Starling mechanism remains uncertain. The results of this study are in line with previous studies of supine exercise, showing a decrease in LV (245,257) and RV (237,258) end-diastolic volumes, particularly during later stages of exercise. Healthy volunteers have been shown to achieve their peak diastolic filling and contractility earlier(245). As a result, LVEDV in healthy volunteers peaked earlier and decreased subsequently. The increase in HR during exercise also reduced diastolic filling time, therefore leading to smaller LV and RV cavity during diastole. It is worth noting that as this study had only assessed 2 stages

of exercise (moderate and high-intensity), it is therefore possible that our data did not capture the initial LV dilatation described in the Frank Starling mechanism.

Although most investigators have reported an exercise-induced increase in stroke volume, there has in fact been evidence that the change in stroke volume was not evident when exercising in the supine position(259,260). Consistent with these studies, we observed no change in LV and RV stroke volumes during exercise. During moderate and high-intensity exercise, the continued rise in cardiac output is therefore best explained by the rise in HR. The differences between our study and previous exCMR studies may be explained by differences in exercise protocol, body posture and types of exercise adopted(239). Methodologic limitations due to different imaging modalities may also account for the lack of consistency in previous studies.

5.5.6 Intra-, inter-observer and inter-scan reproducibility

Intra-observer reproducibility of LV parameters was excellent at all three stages. Similarly, inter-observer reproducibility of LV parameters was also excellent. Although RVESV measurements were least reproducible during exercise, the ejection fraction and cardiac index for RV were however highly reproducible at all 3 stages. The inter-scan reproducibility was less optimal for LV parameters (CV 5-16%) and RVESV (CV 11-24%). The wider interscan variability in results can possibly be explained by the long 16 weeks scan interval between the 1st and 2nd exCMR scans. Although healthy volunteers had no physiological training during that period, other factors such as different loading conditions, diet and temperatures could influence cardiac physiology on a day-to-day basis.

5.6 LIMITATIONS

Cycling whilst lying in a flat, supine position is an unorthodox form of exercise, and skeletal muscle fatigue may lead to premature test termination(239). The exCMR protocol is therefore not suitable for those unable to exercise due to orthopaedic problems or poor conditioning. Knee-to-bore clearance whilst cycling

is also limited by patient height and magnet bore diameter. Occasionally, due to magneto hydromagnetic disturbance, the ECG signal can be distorted, and this can result in ECG miss-triggering. Careful selection of phase whilst cross referencing with the cine images is therefore necessary to identify the true diastole and systole frames. Furthermore, vigorous respiratory movement can also result in blurring or ghosting of images collated across cardiac cycles. Optimal patient preparation, as detailed in the methodology, is therefore vital. The assessment of ventricular volumes in this study was performed during sub-maximal exercise (max HR during image acquisition 131±11bpm), instead of peak exercise capacity. We believe that this does not limit clinical application, as older deconditioned patients often do not achieve their maximal exercise capacity prior to developing symptoms. In fact, the HR achieved using this exCMR protocol was less than the recommended 85% age-predicted maximal heart rate commonly used in defining an adequate treadmill stress test for potential ischaemic heart disease(239,261). Previous echocardiographic studies have however demonstrated similar diagnostic accuracies between supine and treadmill exercise testing, despite a large proportion of patients not achieving the 85% age-predicted maximal HR (241,242,262). Moreover, there has been suggestions that although maximal HR was higher during standing treadmill exercise, systolic BP was higher during a supine bike exercise in echocardiography, resulting in a similar rate-pressure product (i.e. patient achieved similar double product)(263). This technique could also offer serial assessment of ventricular parameters with incremental exercise.

Other limitations of exCMR include its inability to be performed in patients with certain implanted devices. Since most CMR acquisitions are acquired over multiple cardiac cycles, arrhythmias such as atrial fibrillation or premature ventricular contractions may additionally pose a challenge for standard CMR pulse sequences. exCMR is also not as readily available as echocardiography, cannot be performed at the bedside or in some patients with claustrophobia, and is generally a more expensive modality. Furthermore, the study population was small, and the reproducibility should therefore be interpreted with caution. As the study was performed in the supine position, this also limits the interpretation of our results to exercise in the upright position.

5.7 CONCLUSION

This exercise CMR protocol using a novel application of the free-breathing, multi-shot, navigated imaging method allows simultaneous assessment of the left and right ventricular response to *continuous* exercise. Intra and inter-observer readings were highly reproducible. The feasibility of this protocol suggests a future role in the assessment of patients with exercise-related symptoms.

Chapter 6 Feasibility of navigated exercise CMR in asymptomatic patients with significant degenerative mitral regurgitation

6.1 ABSTRACT

Background

Navigated exercise CMR (exCMR) image acquisition techniques for biventricular physiological assessment during continuous physical exercise have recently been shown to be feasible and reproducible. We evaluated the feasibility of exCMR in patients with significant mitral regurgitation (MR) and quantified their exercise-induced changes in ventricular volumes and MR severity.

Methods

12 patients with asymptomatic significant degenerative MR (8 men, age 55±13years, BMI 25±3 kg/m^2) underwent supine cycle ergometer (Lode) exCMR using a free-breathing, multi-shot, navigated, balanced steady-state free precession cine pulse sequence. Target heart rates for both 'light' and 'moderate-intensity' exercise was prescribed based on a pre-CMR cardiopulmonary exercise test. The scan protocol included a short axis ventricular volume stack, two orthogonal left ventricular outflow tract views and aortic phase-contrast flow imaging. Free-breathing cine images were acquired at 3 stages: rest and during steady-state light and moderate-intensity exercise (30-39% and 40-59% of their heart rate reserve, respectively). LV and RV indices were calculated, and MR volume was quantified using the indirect method (Circle cvi[42]).

Results

ExCMR was well tolerated by 10/12 (83%) clinical patients. End-diastolic LV and RV volumes remained unchanged during exercise. Whilst a reduction in end-systolic volume (ESV) was observed in both ventricles, the decrease was only significant during moderate-intensity exercise in the indexed RVESV measurements (44±13ml vs 43±14ml vs 36±12ml, rest vs light vs moderate, $p=0.02$ for light vs moderate). Both the LV and RV stroke volume increased during exercise. LV ejection fraction increased significantly during low intensity exercise before plateauing, whilst the increase in RV ejection fraction was more evident during moderate-intensity exercise. With an increase in exercise intensity, there was generally an augmentation of cardiac output and cardiac index in both the LV and RV. The change in MR volume was variable: with exercise, the MR volume increased in 2/10 patients (20%), decreased in 1/10 patients (10%), remained relatively unchanged in 2/10 patients (20%) and changed dynamically in the remaining 5/10 (50%) patients. MR volume was strongly correlated with MR fraction ($r=0.97$, $p<0.001$) during rest and exercise.

Conclusion

The navigated exCMR protocol is feasible in clinical patients allowing simultaneous assessment of the left and right ventricular responses to continuous exercise. Primary MR appears to be a dynamic entity in this small study although there remains uncertainty about exercise-induced changes in MR. Clinical feasibility of this protocol suggests a future role in the assessment of patients with exercise-related symptoms in larger clinical trials.

6.2 BACKGROUND

The development of symptoms in significant mitral regurgitation (MR) plays a pivotal role in the decision to move toward surgical intervention(30,31). Perception of symptoms is however multifactorial and can be influenced by psychological factors making the detection and objectification challenging(88). Stress imaging with exercise transthoracic echocardiography (i.e. treadmill or supine-bike exercise) can be used to assess the dynamic component of valvular abnormalities and unmask subclinical myocardial dysfunction that could be missed at rest (86–88). Nevertheless, approximately 10% of the patients have non-optimal acoustic windows precluding the use of this modality(89,264). The use of exercise echocardiography to quantitate severity of MR with via the PISA or EROA method can also be challenging in patients with MV prolapse(205). Additionally, non-holosystolic eccentric MR often leads to inaccurate quantitation of MR by echocardiography. Accurate assessment of MR severity and its complications are important, as it not only determines timing and indication for surgical correction, but also carries significant prognostic implications(3,5).

CMR imaging has been the reference standard for the assessment of ventricular volumes and ejection fractions(48). It also has the additional ability to quantify MR with high accuracy and reproducibility (irrespective of MR jet geometry) using a combination of LV volumetric measurements and aortic flow quantification (112,114,121,128). The development of a MRI-compatible cycle ergometer allowed patients to exercise on a supine bike whilst inside the bore of the magnet(235). In the previous chapter, we have demonstrated that exCMR protocol using the free-breathing, multi-shot, navigated imaging method allows simultaneous assessment of the left and right ventricular response during continuous physical exercise and was feasible in healthy volunteers. The practicality and feasibility of this exCMR technique has however yet to be tested on clinical patients, which is often a more challenging group of participants.

The objectives of this clinical study were: 1) to evaluate the clinical feasibility of a navigated exCMR in patients with significant valvular heart disease; 2) to assess exercise-induced changes in ventricular volumes 3) to quantitate the change in MR severity with exercise and 4) to examine the predictors of exercise-induced changes in MR severity in patients with normal LV function.

Hypothesis: The navigated exCMR protocol is feasible in patients with significant valvular heart disease, and MR severity worsens with exercise.

6.3 METHODS

6.3.1 Study design and population

Clinical application of this technique was examined in 12 patients with significant MR, all prospectively recruited from the valvular heart disease clinic at Leeds Teaching Hospitals NHS Trust. Inclusion criteria included: moderate-severe or severe MR on echocardiography, LV ejection fraction >55%, NHYA Class I and had a baseline clinical treadmill CPET. Exclusion criteria included: contraindications to exercise stress testing according to AHA guidelines(239), presence of AF or other valvular heart disease, presence of previous myocardial infarction or significant respiratory disease, inability to exercise and contraindications to CMR. Baseline clinical and demographic data were recorded for all patients. The study was approved by a local ethics committee (Yorkshire & The Humber-Leeds West 12/YH/0551) and complied with the Declaration of Helsinki. All participants provided written informed consent (See Appendix).

All patients underwent exCMR on a supine cycle ergometer and the use of ß-adrenergic blocking medication was discontinued 48 hours before the test. All other cardiovascular drugs were maintained. CMR was performed on a 1.5 Tesla MRI system (Ingenia, Philips Healthcare, Best, Netherlands), with a 70cm bore and equipped with a 28-channel coil. Free-breathing cine images were acquired during continuous exercise. In our institution treadmill CPET is used clinically in patients with significant MR and we utilized these data to prescribe the

individualized target HR during exCMR. To allow for the lower HR response in supine cycling compared to upright treadmill exercise and the reduced exercise tolerance seen in patients with severe MR, the prescribed HR had to be altered from healthy volunteers, used in our previous work. Exercise intensity was individualized to the HR corresponding to 30-39% and 40-59% of their heart rate reserve (HRR), corresponding to 'light' and 'moderate'-intensity exercise according to the American College of Sports Medicine guidelines(265). HRR was calculated based on this formula: resting HR on CPET + [*x*% of (max HR achieved on treadmill CPET – resting HR)]; where *x* is the target % of HRR (265).

6.3.2 Exercise CMR protocol and image acquisition

Exercise whilst in the bore of the magnet was conducted on a supine MRI-compatible cycle ergometer (Lode BV, Groningen, The Netherlands). Optimal patient preparation included instructions on consistent thoracic breathing, use of handrail to ensure trunk stability, skin preparation to maximize interface between electrode and skin, and securing vector ECG connections onto anterior chest wall with tape to ensure quality recording of ECG. A BP cuff was placed on the left arm. Both the surface coil and torso pad were then firmly secured onto the participants with elastic Velcro® straps. The MRI table was advanced whilst patients performed a short bout of unloaded exercise to ensure that their knees did not contact the external casing of the MRI scanner during pedalling.

During each stage of exercise: 1) Free-breathing cine images were acquired during continuous exercise; 2) Free-breathing phase contrast flow imaging were acquired immediately following transient cessation of exercise. Free-breathing images were acquired at 3-stages, at rest and then during steady-state exercise at two intensities: 'light' and 'moderate'-intensity, as defined above. Exercise began with a 2min warm-up at a power output of 0W (unloaded). Work rate was incrementally increased by 10-20W until the target HR for 'light'-intensity exercise was achieved. Verbal feedback was constantly given to patients and cycling cadence was maintained between 60-70rpm. Following a rest of 2 minutes (during which free-breathing PC images were acquired), a second bout of exercise was undertaken until the target HR for 'moderate'-intensity exercise was

achieved. Heart rate and rhythm were continuously monitored, and BP was recorded at all stages. Each stage of exercise was maintained for 5-7mins (2 minutes to achieve steady-state and approximately 3-5mins of cine image acquisition). Cine imaging was only performed during steady-state conditions, when HR was maintained at reasonably constant levels. Standard criteria for termination prior to achieving target HR were observed including: participant's request, limiting symptoms, significant arrhythmias, drop in systolic BP >10mmHg, severe hypertension (systolic arterial pressure >240mmHg or diastolic arterial pressure >110mmHg) or any ST-segment elevation of more than 2mm.

The scan protocol included standard long axis views (vertical, horizontal long axis), two orthogonal LVOT views, a short axis ventricular volume stack and aortic phase-contrast flow imaging. Cine imaging was performed using a free-breathing, multi-shot, respiratory-navigated, balanced steady-state free precession pulse sequence. Respiratory echo-based navigator was placed on the right hemi-diaphragm with a 5mm gating window and continuous gating level drift activated. A cylindrical MR radiofrequency excitation pulse from which a 1-dimensional projection of the lung-liver interface was generated and was used to infer the breathing phase. Cartesian sampling was used, and the acquired k-space lines were only accepted for image reconstruction if the right hemi-diaphragm position was within the gating window during end-expiratory phase. Other bSSFP scan parameters were as follows: typical FOV 320x320mm, TR 2.8msec, TE 1.4msec, flip angle 60°, temporal resolution 33msec, SENSE factor 2, multi-shot TFE factor 11, TFE acquisition duration 30.4ms, phase percentage 50%, slice thickness 10mm, 0mm gap, 30 phases, in-plane spatial resolution 2.4×2.4mm, matrix 132x106.

Aortic flow data was acquired using a free-breathing, retrospectively gated PC velocity encoding technique which was sensitized for flow in the through plane direction. The region of interest was planned at the sino-tubular junction at end diastole, orthogonal to the aortic valve jet. VENC was typically set at 150 cm/s on the baseline scan, 250cm/s during 'light' intensity exercise and 350cm/s during 'moderate' intensity exercise. If aliasing occurred at the pre-set VENC, sequential

phase contrast imaging was performed at increasing VENC settings until the aliasing artefact had disappeared. Other scan parameters for gradient echo PC imaging were as follows: typical FOV 350x240mm, TR 5.2msec, TE 3.2msec, flip angle 15°, number of signal averages 1, SENSE factor 2, multi-shot TFE factor 2, TFE acquisition duration 20.6ms, slice thickness 8mm, 30 phases, phase percentage 100%, in-plane spatial resolution 2.5×2.5mm, matrix 140x94, Cartesian sampling, and typical acquisition times were 12-21 seconds for free-breathing sequences.

6.3.3 CMR Analysis

CMR analysis was performed by an independent operator (PC). Left and right ventricular volumes, ejection fractions, stroke volume and cardiac output were calculated based on the general methodology described in Chapter 2.

MR volume and MR fraction were both quantified using the below two methods

i) Flow method: difference between LV stroke volume and aortic forward flow volume

$$MR\ volume_{flow} = LV_{SV} - Aortic_{forward\ flow} = [LV_{EDV} - LV_{ESV}] - [Flow\ SV_{aortic}]$$

$$MR\ fraction_{flow} = \frac{\text{MR Volume}}{LV_{sv}}\ x\ 100\%$$

ii) Volumetric method: difference between LV stroke volume and RV stroke volume

$$MR\ volume_{volumetric} = LV_{SV} - RV_{SV} = [LV_{EDV} - LV_{ESV}] - [RV_{EDV} - RV_{ESV}]$$

$$MR\ fraction_{volumetric} = \frac{\text{MR Volume}}{LV_{sv}}\ x\ 100\%$$

6.3.4 Statistical Analysis

General statistical analysis were as described in Chapter 2. Repeated measures ANOVA with Bonferroni post-test analysis was used to compare data between

rest and different stages of exercise. Linear regression analysis was applied to study the correlation between severity of MR (at rest and during exercise) and ventricular/flow parameters. To determine independent predictors of the degree of MR 1) at rest 2) during exercise and 3) change in the MR volume (ΔMR volume) with exercise, stepwise multiple linear regression was performed. All variables with a p value <0.10 were included in the multivariate model. $p<0.05$ was considered statistically significant.

6.4 RESULTS

6.4.1 Patient characteristics

Of 12 patients with severe MR, 10 patients (8 men, age 55±13years, BMI 25±3 kg/m^2) completed the full study protocol. exCMR had to be abandoned in 2 patients due to a significant hypotensive response (n=1) and inability to complete the exercise protocol due to leg fatigue (n=1). Quantitative measurements were obtained in all the remaining 10 patients. Mechanism of MR was degenerative MV (posterior leaflet prolapse (n= 6; 60%), anterior leaflet prolapse (n=1, 10%), bi-leaflet prolapse (n=2, 20%) and flail leaflet (n=1, 10%). Severity of MR according to baseline echocardiography evaluation was moderate-severe in 4/10 patients (40%) and severe in 6/10 patients (60%). Some patients were on regular use of ACE-inhibitors (n=3) and ß-blockers (n=1). Only the use of ß-blockers was discontinued 48hours before the study.

HR increased throughout exercise (74±7bpm vs 109±9bpm vs 118±12bpm; baseline vs light $p<0.001$, light vs moderate $p=0.003$, baseline vs moderate $p<0.001$). Systolic BP was significantly higher during moderate intensity exercise than at baseline (149±12mmHg vs 123±13mmHg; $p=0.001$), whilst diastolic BP remained constant (79±10mmHg vs 86±9mmHg vs 78±15mmHg; $p=1.00$). Mean work rate for light and moderate-intensity exercise was 40±23W and 50±24W, respectively. No subjects developed atrial fibrillation or supraventricular tachycardia during exercise.

6.4.2 Baseline CMR data

CMR data for all clinical patients are described in Table 5.1. Baseline LV ejection fraction was 58±3% and all patients had LV ejection fraction of >55% at baseline. According to CMR criteria for MR classification (112) MR was graded as severe in 1/10 patients (10%), moderate-severe in 7/10 patients (70%), only moderate in 2/10 patients (20%).

Table 6.1 Volumetric and flow data at baseline, and during light and moderate-intensity exercise in patients with significant mitral regurgitation

Cardiovascular variables	Baseline	Light Intensity	Moderate Intensity	P value (Baseline vs Light)	P value (Light vs Moderate)	P value (Baseline vs Moderate)
LVEDV (ml)	196±31	206±34	202±38	0.30	0.72	1.00
LVEDV (indexed), ml/m^2	102±18	107±21	104±22	0.31	0.59	1.00
LVESV (ml)	82±13	74±15	73±19	0.18	1.00	0.16
LVESV (indexed), ml/m^2	42±8	38±9	38±10	0.19	1.00	0.15
LVSV (ml)	114±20	132±23	129±21	**0.001**	0.57	**< 0.001**
LVSV (indexed), ml/m^2	59±11	69±14	67±12	**0.003**	0.55	**0.001**
LVEF (%)	58±3	64±4	64±4	**0.003**	1.00	**0.007**
LV cardiac output, ml/min	8522± 1946	14449± 2913	15228± 2877	**< 0.001**	**0.03**	**< 0.001**
LV cardiac index, ml/min/m^2	4393± 1003	7482± 1713	7891± 1755	**< 0.001**	**0.03**	**< 0.001**
RVEDV (ml)	176±44	187±48	177±45	0.31	0.53	1.00
RVEDV (indexed), ml/m^2	90±22	96±25	91±22	0.33	0.56	1.00

RVESV (ml)	86±27	83±29	71±24	1.00	**0.03**	**0.003**
RVESV (indexed), ml/m^2	44±13	43±14	36±12	0.75	**0.02**	**0.003**
RVSV (ml)	90±18	105±27	106±23	0.10	1.00	0.11
RVSV (indexed), ml/m^2	46±9	54±15	55±11	0.13	1.00	0.14
RVEF (%)	52±4	56±8	60±5	0.16	0.43	**0.002**
RV cardiac output, ml/min	6733± 1815	11414± 3114	12452± 2503	**< 0.001**	0.71	**< 0.001**
RV cardiac index, ml/min/m^2	3467± 937	5894± 1712	6422± 1352	**0.001**	0.77	**< 0.001**
Aortic Flow						
Ao forward flow (ml)	75±11	87±7	85±10	**0.007**	1.00	**0.03**
Ao backward flow (ml)	4±3	4±2	6±4	1.00	0.35	0.40
Ao volume (ml)	71±13	83±7	79±11	**0.01**	0.76	0.18
Ao RF (%)	5.9±4.5	4.7±2.5	7.8±4	0.96	0.29	1.00
Ao max PG (mmHg)	6.3±1.9	11.1±5.9	19±16	0.06	0.38	0.09
Ao mean PG (mmHg)	1.5±0.5	2.9±2.0	3.8±3.1	0.08	1.00	0.07
Ao peak velocity (m/s)	1.3±0.2	1.6±0.4	2.0±0.8	**0.04**	0.30	**0.02**
Mitral regurgitation						
MR volume$_{flow}$ (ml)	40±19	46±22	44±22	0.41	1.00	0.84
MR fraction$_{flow}$ (%)	33±12	33±12	33±13	1.00	1.00	1.00

MR volume$_{volumetric}$ (ml)	24±10	28±15	23±16	1.00	1.00	1.00
MR fraction$_{volumetric}$ (%)	21±8	21±13	17±12	1.00	1.00	1.00

Data as mean±SD. ANOVA with Bonferroni correction was used to compare continuous data between groups. LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVSV, left ventricular stroke volume; LVEF, left ventricular ejection fraction; LV, left ventricle; RVEDV, right ventricular end-diastolic volume; RVESV, right ventricular end-systolic volume; RVSV, right ventricular stroke volume; RVEF, right ventricular ejection fraction; RV, right ventricle; Ao, aortic; RF, regurgitant fraction; PG, pressure gradient; MR, mitral regurgitation.

6.4.3 Left and right ventricular parameters during exercise

The changes in ventricular volumes during exercise are plotted in Figure 5.1. There was no significant change in the LVEDV during exercise, and despite a downward trend of LVESV, this was not significant. Both LV stroke volume (indexed) and LV ejection fraction increased significantly during light-intensity exercise, with no further increase during moderate-intensity exercise (Figure 5.2). When compared to baseline, LV stroke volume increased significantly when moderate-intensity exercise was achieved (15+-8ml, $p<0.001$). The augmentation of LV cardiac output and cardiac index was also apparent with incremental exercise (Figure 5.3). None of the patients sustained a significant drop in ejection fraction during exercise.

When considering the RV parameters, there was no significant exercise-induced changes in the end-diastolic volume. During moderate-intensity exercise however, RVESV was significantly smaller than at baseline. RV ejection fraction was significantly increased above rest during moderate-intensity exercise. Similar to the left ventricle, there was a significant increase in RV stroke volume during exercise (Figure 5.2). RV cardiac output and RV cardiac index increases significantly during light-intensity exercise and appear to plateau during moderate-intensity exercise.

LV stroke volume significantly increased by 18±10ml during light intensity exercise, and despite a small decrease of -3.4±7.6ml when moderate-intensity of exercise was achieved, this was not significant. In contrast, absolute change in RV stroke volume was not significant: 15±18ml (baseline vs light), 18±22ml (light vs moderate), and 17±21ml (baseline vs moderate). The contractile reserve was 10.5±8.6% for LV ejection fraction and 13.4±8.6% for LV stroke volume. Contractile reserve of >4% rise in LV ejection fraction was present in 80% (n=8) of the patients, and absent in 20% (n=2) of the patients. On the other hand, contractile reserve of >20% rise in LV stroke volume was present in 20% (n=2) of the patients and absent in 80% (n=8) of the patients.

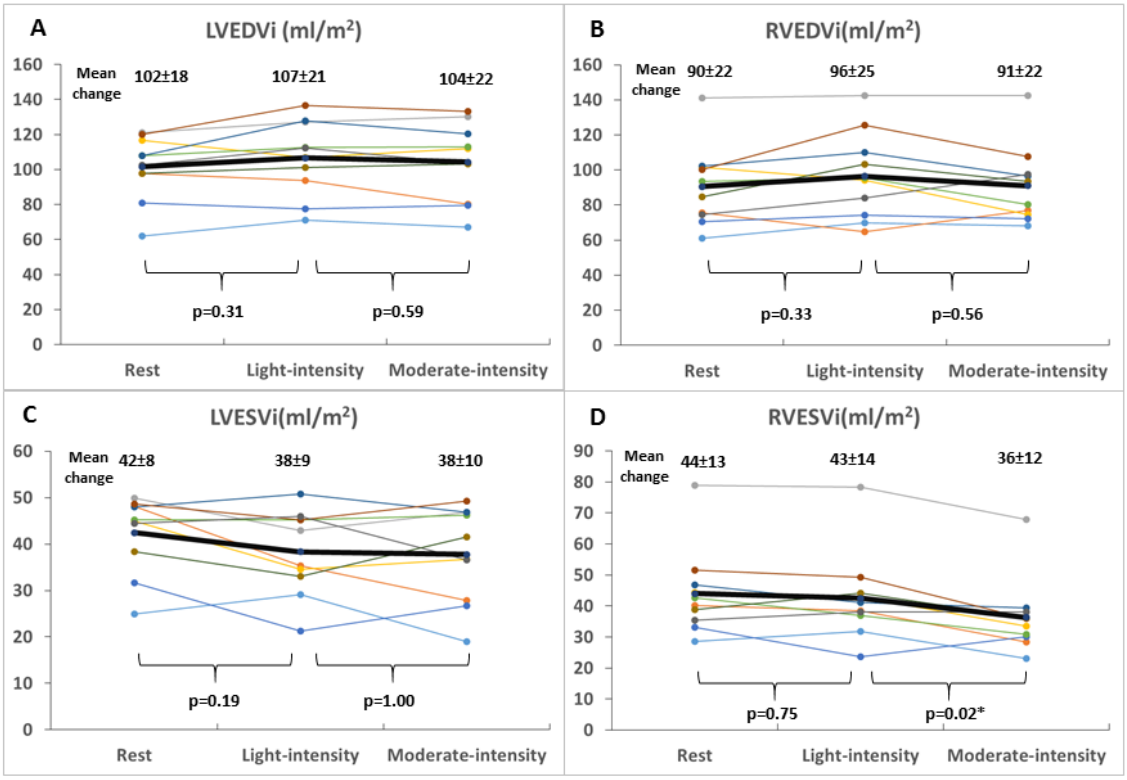

Figure 6.1 Ventricular volumes during exercise in patients with significant mitral regurgitation

End-diastolic and end-systolic volumes of left (Panel A and C) and right (Panel B and D) ventricle during exercise. LVEDVi, indexed left ventricular end-diastolic volume; LVESVi, indexed left ventricular end-systolic volume; RVEDVi, indexed right ventricular end-diastolic volume; RVESVi, indexed right ventricular end-systolic volume. Coloured lines represent individual patient data and thickened black line indicate mean measurements at all stages. Asterisks denote statistically significant differences ($p<0.05$)

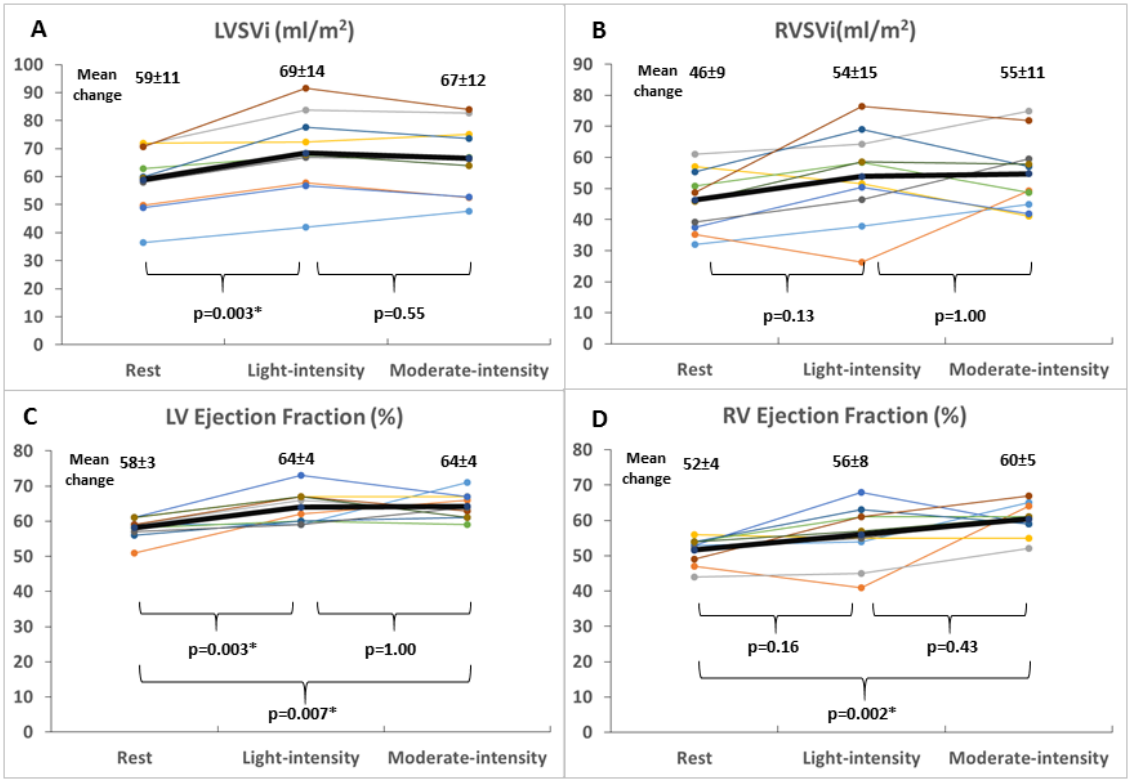

Figure 6.2 Exercise cardiac reserve in patients with significant mitral regurgitation

Left and right ventricular stroke volume (Panel A and B); left and right ventricular ejection fraction (Panel C and D) during exercise. LVSVi, indexed left ventricular stroke volume; LV, left ventricular; RVSVi, indexed right ventricular stroke volume; RV, right ventricular. Coloured lines represent individual patient data and thickened black line indicate mean measurements at all stages. Asterisks denote statistically significant differences ($p<0.05$)

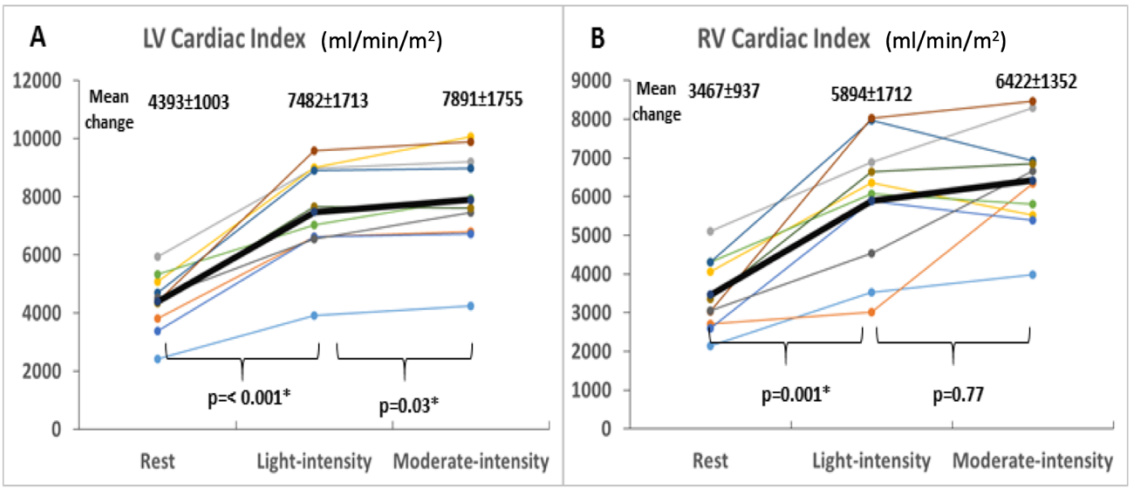

Figure 6.3 Exercise cardiac index in patients with significant mitral regurgitation

Left and right ventricular cardiac index (Panel A and B) during exercise. LV, left ventricular; RV, right ventricular. Coloured lines represent individual patient data and thickened black line indicate mean measurements at all stages. Asterisks denote statistically significant differences ($p<0.05$)

6.4.4 Aortic flow parameters during exercise

During phase-contrast imaging of the aortic flow, HR increased throughout exercise. The increase in HR from light- to moderate-intensity exercise was however not significant (72±9bpm vs 91±12bpm vs 97±10bpm; baseline vs light $p<0.001$, light vs moderate $p=0.43$, baseline vs moderate $p<0.001$). Both aortic forward flow and peak velocity increased significantly with light-intensity exercise and appear to plateau thereafter (Figure 5.4). Despite an increased trend of pressure gradient though the aortic valve, the changes were not significant.

6.4.5 MR severity and exercise-induced changes in MR

As the baseline data for MR volume and fraction derived from the *flow* method appear to fall within the expected moderate-severe MR category (*MR volume*$_{flow}$ 40±19ml; *MR fraction*$_{flow}$ 33±12% vs MR volume$_{volumetric}$ 24±10ml; MR fraction$_{volumetric}$ 21±8%), these measurements were deemed to be more physiologically concordant with the echo grading. This chapter will therefore primarily use the data of *MR volume*$_{flow}$ as a reference point to describe correlations in the next section.

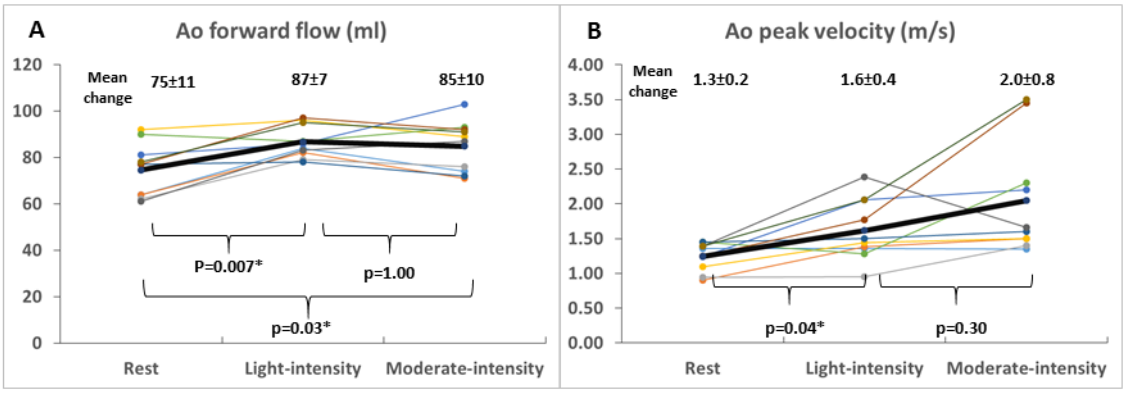

Figure 6.4 Exercise aortic parameters in patients with significant mitral regurgitation

Aortic forward flow (Panel A) and aortic peak velocity (Panel B) during exercise. Ao; aortic. Coloured lines represent individual patient data and thickened black line indicate mean measurements at all stages. Asterisks denote statistically significant differences ($p<0.05$)

When considered as a whole, there was no significant exercise-induced change in MR volume or MR fraction with both the flow and volumetric method (Table 5.1). Although these changes were not significant, the averaged MR $volume_{flow}$ increased from 40±19ml to 46±22ml during light-intensity exercise and plateaued at 44±22ml during moderate-intensity exercise. Overall MR fraction was unchanged throughout exercise. The absolute change in MR $volume_{flow}$ was 6±11ml (baseline vs light; p=0.84), -1.5±12ml (light vs moderate; p=0.41), and 4.5±12ml (baseline vs moderate; p=1.00), whilst the change in MR $fraction_{flow}$ was -0.6±8.5% (baseline vs light; p=1.00), 0.1±10.3% (light vs moderate; p=1.00), and -0.5±9.8% (baseline vs moderate; p=1.00). On the other hand, absolute change in MR $volume_{volumetric}$ was 3.4±14ml (baseline vs light), -5.2±23ml (light vs moderate), and -1.8±19ml (baseline vs moderate).

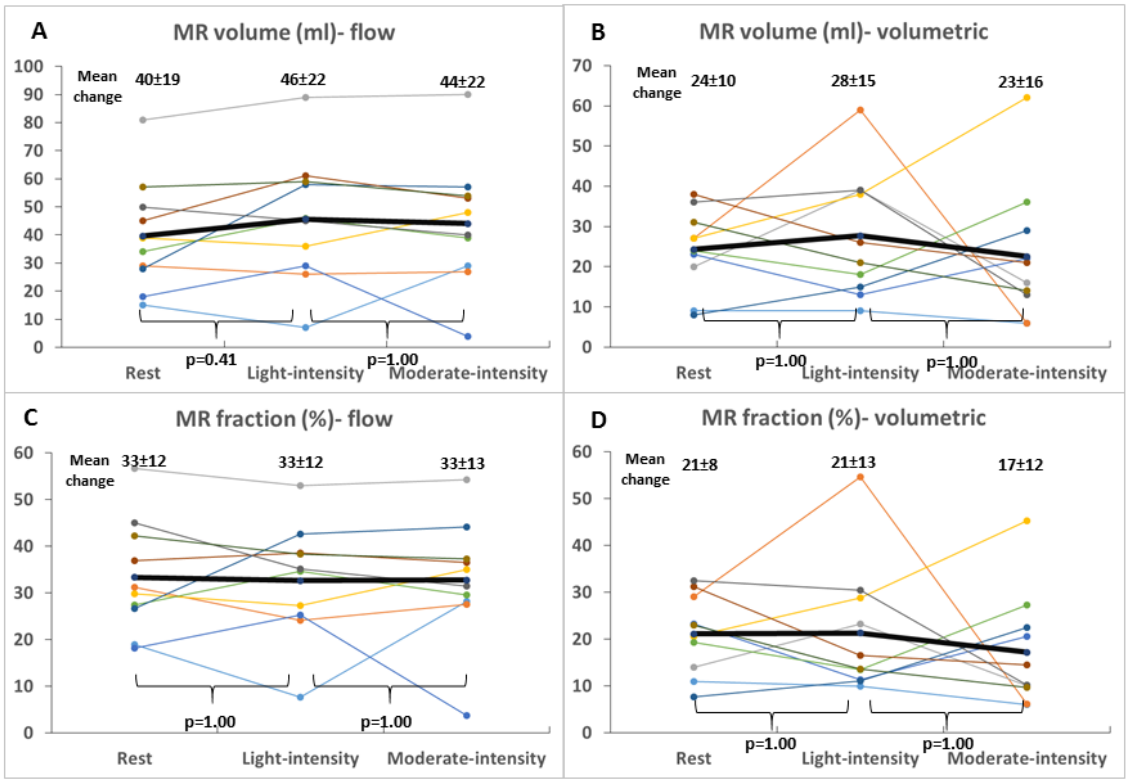

Figure 6.5 Severity of mitral regurgitation during exercise

MR $volume_{flow}$ and MR $fraction_{flow}$ (Panel A and C) and MR $volume_{volumetric}$ and MR $fraction_{volumetric}$ (Panel B and D) during exercise. MR, mitral regurgitation. Coloured lines represent individual patient data and thickened black line indicate mean measurements at all stages. Asterisks denote statistically significant differences ($p<0.05$)

The change in MR volume or fraction was however found to be variable in individual patients. Figure 5.5 demonstrates the exercise-induced changes in MR severity for individual patients. With exercise, the MR $volume_{flow}$ increased in 2/10 patients (20%), decreased in 1/10 patients (10%), remained relatively unchanged in 2/10 patients (20%) and changed dynamically in the remaining patients [(increased then plateaued (n=2); increased then decreased (n=1); decreased then increased (n=2)]. Similar individual variable changes were seen with the volumetric method, where MR $volume_{volumetric}$ increased in 2/10 patients (20%), decreased in 2/10 patients (20%), remained relatively unchanged in 1/10 patients (10%) and changed dynamically in the remaining patients [(increased then decreased (n=3); decreased then increased (n=2)]. Individual variable changes were also seen when MR fraction (flow and volumetric method) was considered, although the trend of change in MR fraction did not correspond with their trend of change in MR volume.

During light-intensity exercise, MR severity was graded as severe in 1/10 patients (10%) moderate-severe in 6/10 patients (60%), moderate in 2/10 patients (20%) and mild in 1/10 patients (10%). During moderate intensity exercise, MR severity was graded as severe in 1/10 patients (10%) moderate-severe in 8/10 patients (80%), moderate in 0/10 patients (0%) and mild in 1/10 patients (10%). With increasing exercise, an increase of ≥ 15ml MR volume was observed in 1/10 patients with the flow method and 2/10 patients with the volumetric method.

6.4.6 Predictors of the degree of MR at baseline

LV and RV end-diastolic volume, stroke volume and cardiac output were positively associated with severity of MR at baseline. No significant associations were found between MR $volume_{flow}$ at rest and LV/RV ejection fraction, age or aortic flow parameters. Multivariate analysis of MR predictors showed LV end-diastolic volume to be the most important predictor of MR severity at baseline. MR $volume_{flow}$ correlated very well with MR $fraction_{flow}$ ($r=0.97$, $p<0.001$). Correlations with both MR $volume_{volumetric}$ ($r=0.39$, $p=0.26$) and MR $fraction_{volumetric}$ ($r=0.13$, $p=0.71$) were however poor.

6.4.7 Predictors of the degree of MR during moderate-intensity exercise

LV and RV end-diastolic volume, stroke volume and cardiac output were again positively associated with severity of MR during moderate-intensity exercise (Table 5.2). No significant associations were found between MR $volume_{flow}$ at rest and LV/RV ejection fraction, aortic flow parameters or systolic BP. LV stroke volume was found to be the strongest predictor of MR severity during exercise ($r^2=0.88$, $p=0.001$). Yet again, MR $volume_{flow}$ correlates very well with MR $fraction_{flow}$ during exercise ($r=0.96$, $p<0.001$). Correlations with both MR $volume_{volumetric}$ ($r=0.10$, $p=0.77$) and MR $fraction_{volumetric}$ ($r=0.02$, $p=0.93$) remained poor.

Table 6.2 Logistic regression for the severity of MR (MR volume$_{flow}$) during moderate-intensity exercise

UNIVARIATE REGRESSION ANALYSIS	R	R^2	F value	Standardised Co-efficient Beta	Beta CI Lower	Beta CI upper	Univariate P value
Age	0.47	0.22	2.2	-0.47	-2.12	0.44	0.16
Systolic BP	0.12	0.01	0.12	0.12	-1.2	1.68	0.73
CMR characteristics							
LVEDV (ml)	**0.84**	0.71	20.5	0.84	0.24	0.75	**0.001**
LVEDVi (ml)	**0.78**	0.61	12.9	0.78	0.28	1.31	**0.006**
LVESV (ml)	**0.74**	0.54	9.6	0.74	0.22	1.52	**0.01**
LVESVi (ml)	**0.72**	0.52	8.9	0.72	0.36	2.85	**0.01**
LVSV (ml)	**0.88**	0.77	27.5	0.88	0.52	1.35	**<0.001**
LVSVi (ml)	**0.81**	0.64	14.7	0.80	0.57	2.30	**0.004**
LVEF (%)	0.47	0.22	2.30	-0.47	-7.54	1.55	0.16
LV cardiac output, ml/min	**0.68**	0.47	7.16	0.68	0.0007	0.01	**0.02**
LV cardiac index, ml/min/m2	0.61	0.37	4.80	0.61	-0.0004	0.01	**0.05**
RVEDV (ml)	**0.81**	0.65	15.4	0.81	0.16	0.64	**0.004**
RVEDVi (ml)	**0.86**	0.73	22.7	0.86	0.44	1.28	**0.001**
RVESV (ml)	**0.79**	0.63	13.7	0.79	0.27	1.18	**0.005**
RVESVi (ml)	**0.83**	0.70	18.7	0.83	0.72	2.38	**0.002**
RVSV (ml)	**0.73**	0.54	9.5	0.73	0.18	1.27	**0.01**
RVSVi (ml/m^2)	**0.76**	0.58	11.3	0.76	0.46	2.47	**0.009**
RVEF (%)	0.47	0.22	2.3	-0.47	-6.02	1.19	0.16
RV cardiac output, ml/min	**0.71**	0.51	8.2	0.71	0.001	0.01	**0.02**
RV cardiac index, ml/min/m^2	**0.70**	0.49	7.7	0.70	0.002	0.021	**0.02**

Aortic valve parameters (CMR)							
Aortic forward flow (ml)	0.36	0.13	1.2	-0.36	-2.35	0.82	0.29
Ao backflow (ml)	0.29	0.08	0.74	0.29	-2.81	6.20	0.41
Ao net volume (ml)	0.44	0.19	1.9	-0.44	-2.33	0.56	0.19
Ao Rfraction (ml)	0.34	0.11	1.1	0.34	-2.15	5.69	0.32
Aortic max PG (mmHg)	0.06	0.003	0.02	0.05	-1.07	1.24	0.86
Mean gradient, (mmHg)	0.01	0.0002	0.001	-0.01	-5.9	5.7	0.96
Ao peak vel (m/s)	0.01	0.0003	0.003	0.01	-22.0	23.1	0.95
MR $fraction_{flow}$ (%) (moderate-intensity exercise)	**0.96**	0.92	97.0	0.96	1.29	2.08	**<0.001**
MR $volume_{volumetric}$ (ml) (moderate-intensity exercise)	0.10	0.01	0.09	0.10	-0.95	1.23	0.77
MR $fraction_{volumetric}$ (%) (moderate-intensity exercise)	0.02	0.0008	0.006	-0.02	-1.6	1.4	0.93

BP, blood pressure; LVEDV, left ventricular end-diastolic volume; i, indexed; LVESV, left ventricular end-systolic volume; LVSV, left ventricular stroke volume; LVEF, left ventricular ejection fraction; RVEDV, right ventricular end-diastolic volume; RVESV, right ventricular end-systolic volume; RVSV, right ventricular stroke volume; RVEF, right ventricular ejection fraction; Ao, aortic; PG, pressure gradient; MR, mitral regurgitation

6.4.8 Predictors of exercise-induced increased MR severity

The decrease in aortic net flow (r=-0.65, p=0.04) and a younger age (r=-0.61, p=0.05) were associated with an increased MR severity during exercise (Table 5.3). The increase in MR severity also appears to correlate weakly with the exercise-induced increase in both LV end-diastolic volume (r= 0.53, p=0.11) and LV stroke volume (r=0.50, p=0.14), although not significant. The change in LV end-systolic volume, LV stroke volume and ejection fraction during exercise were not associated with exercise-induced change in MR severity. The change in MR during exercise was also unrelated to baseline MR severity. Independent predictors of MR changes during exercise were aortic net flow and age.

Table 6.3 Logistic regression for the exercise-induced change in MR volume$_{flow}$

UNIVARIATE REGRESSION ANALYSIS	R	R^2	F value	Standardised Co-efficient Beta	Beta CI Lower	Beta CI upper	Univariate P value
Age	**-0.61**	0.37	4.8	-0.61	-1.20	0.03	**0.05**
Systolic BP	0.01	0.0001	0.0009	0.01	-0.79	0.82	0.97
CMR characteristics (moderate-intensity exercise)							
LVEDV (ml)	0.22	0.05	0.42	0.22	-0.18	0.32	0.53
LVEDVi (ml)	0.37	0.13	1.27	0.37	-0.21	0.63	0.29
LVESV (ml)	0.19	0.03	0.30	0.19	-0.39	0.64	0.59
LVESVi (ml)	0.33	0.10	0.98	0.33	-0.53	1.34	0.35
LVSV (ml)	0.22	0.04	0.41	0.22	-0.33	0.59	0.53
LVSVi (ml)	0.38	0.15	1.42	0.38	-0.35	1.11	0.26
LVEF (%)	0.12	0.01	0.12	-0.12	-3.24	2.37	0.73
LV cardiac output, ml/min	0.10	0.01	0.09	0.10	-0.003	0.003	0.76
LV cardiac index, ml/min/m2	0.26	0.06	0.59	0.26	-0.003	0.007	0.46
RVEDV (ml)	0.04	0.002	0.01	0.04	-0.21	0.23	0.90
RVEDVi (ml)	0.17	0.03	0.25	0.17	-0.34	0.54	0.63
RVESV (ml)	0.05	0.003	0.02	0.05	-0.38	0.43	0.87
RVESVi (ml)	0.15	0.02	0.19	0.15	-0.66	0.98	0.66
RVSV (ml)	0.02	0.0005	0.004	0.02	-0.42	0.45	0.94
RVSVi (ml/m^2)	0.16	0.02	0.23	0.16	-0.66	1.02	0.64
RVEF (%)	0.07	0.006	0.05	-0.07	-2.46	2.02	0.82
RV cardiac output, ml/min	0.08	0.007	0.05	-0.08	-0.004	0.003	0.81

RV cardiac index, ml/min/m^2	0.08	0.007	0.06	0.08	-0.006	0.008	0.80
ΔLVEDV	**0.53**	0.28	3.2	0.53	-0.2	1.6	0.11
ΔLVESV	0.39	0.15	1.4	0.39	-0.6	2.0	0.26
ΔLVSV	**0.50**	0.24	2.5	0.49	-0.6	3.3	0.14
ΔLVEF	0.43	0.18	1.8	-0.43	-5.8	1.4	0.21
MR $volume_{flow}$ (baseline)	0.05	0.003	0.02	-0.05	-0.5	0.4	0.87
Aortic valve parameters (CMR)							
Aortic forward flow (ml)	**-0.60**	0.36	4.5	-0.60	-1.43	0.05	**0.06**
Ao backflow (ml)	0.24	0.05	0.5	0.24	-1.7	3.2	0.49
Ao net volume (ml)	**-0.65**	0.42	5.8	-0.65	-1.3	-0.03	**0.04**
Ao Rfraction (ml)	0.35	0.12	1.1	0.35	-1.1	3.1	0.31
Aortic max PG (mmHg)	0.21	0.04	0.4	-0.21	-0.78	0.45	0.55
Mean gradient, (mmHg)	0.33	0.11	1.0	-0.33	-4.3	1.6	0.33
Ao peak vel (m/s)	0.24	0.06	0.5	-0.24	-15.7	8.29	0.49

BP, blood pressure; LVEDV, left ventricular end-diastolic volume; i, indexed; LVESV, left ventricular end-systolic volume; LVSV, left ventricular stroke volume; LVEF, left ventricular ejection fraction; RVEDV, right ventricular end-diastolic volume; RVESV, right ventricular end-systolic volume; RVSV, right ventricular stroke volume; RVEF, right ventricular ejection fraction; Ao, aortic; PG, pressure gradient; MR, mitral regurgitation. Symbol Δ denotes absolute change (from baseline to exercise)

6.5 DISCUSSION

This study demonstrated 1) the clinical feasibility of this exCMR imaging method in assessing cardiac physiology in a challenging group of patients with significant valvular heart disease 2) that both LV and RV stroke volume increased during light-intensity exercise and plateaued thereafter 3) although MR appears to be a dynamic entity in this small study, there remains uncertainty in the understanding of exercise-induced changes in MR and if these changes were also influenced by a scan-rescan variation.

To the best of our knowledge, this is the first study to describe the feasibility of navigated exCMR recordings in clinical valvular heart disease patients. The completion of navigated exCMR was feasible in 10/12 patients (83%). One scan was abandoned due to significant hypotension, a valid criterion for termination of exercise testing, whilst one other scan was stopped due to muscular exhaustion. This particular patient had a height of >190cm which resulted in an uncomfortable cycling regime due to knee contact with the MR scanner external casing leading to the premature termination of the test.

6.5.1 Image acquisition techniques

A key strength of our study was the ability to image during continuous exercise in a patient group with significant valvular heart disease. Current available image acquisition techniques used with the MRI cycle ergometer have either involved a brief period of exercise cessation(236) or required a breath-hold protocol(225,237) in order to reduce excessive motion artefacts and avoid poor ECG signal. We have previously demonstrated that the application of respiratory-navigated technique in exCMR has the potential to overcome respiratory motion which can be quite significant during strenuous exercise. This technique was proven to be feasible in healthy volunteers and the images acquired were both analysable and reproducible. Moreover, this imaging technique allowed serial assessment of cardiac function with incremental exercise and a further advantage is that image analysis can be performed on commercially available

software a limitation of current real-time imaging techniques. With this navigated exCMR method, time lapse between exercise and imaging can be eliminated and this may allow a more accurate assessment of changes in cardiac physiology during exertion. It is also worth noting that our 70cm MRI bore magnet (unlike those in other studies(238) which are only 60cm bore) makes the cycling much easier for patients. In the current era, stress CMR may be performed with either supine ergometer exercise(227,238) or intravenous inotropes, usually dobutamine using a graded protocol(266). Dobutamine stress echo is however not useful in the evaluation of MR due to its reduction in pre-load and afterload and beneficial effect on the MR(267,268). Physical exercise is therefore deemed to be more physiological and able to reflect patients' day-to-day exertional activities.

6.5.2 Current exercise modalities

The widely available exercise echocardiography can be performed using either a standing treadmill or bicycle ergometer, and image acquisition takes place rapidly after exercise cessation(269). With supine bicycle exercise, imaging may be performed during the different stages of exercise and therefore circumventing the rapid changes in heart rate and loading conditions. (270,271). Current available echocardiographic studies are often limited by suboptimal echogenicity (up to 8%) and difficulty in assessing PISA/EROA during exercise (205). Optimal flow convergence region is mandatory in order to achieve accurate quantification of MR volume. Furthermore, echocardiography frequently overestimates MR severity (272), displaying a larger regurgitant volume. Some studies have suggested that CMR is more accurate than echocardiography in assessing the severity of MR, especially in those with prolapsing leaflets and eccentric/multiple jets (114,115,129). In our study, the use of a highly accurate CMR tool therefore enables a more reliable quantitation of MR volume irrespective of MR jet geometry.

6.5.3 Exercise-induced changes in volumetric measurements

The effects of left and right ventricular volumes during physical exercise in patients with significant MR remains relatively unexplored. In the context of

emptying into a low impedance LA, the LVEF can be normal for a long period whereas LV contractility (i.e the innate ability of the myocardium to generate force) might already be significantly reduced(66). In our study, LV volumes were unchanged during light and moderate intensity exercise. In general, EDV indicates that there is a regurgitation load and is always greater than normal in chronic severe MR. ESV on the other hand, indicates the ventricular response to the regurgitation lesion. The lack of EDV reduction allowed augmentation of total stroke volume which therefore maintains forward stroke volume near normal, whilst the absence of end-systolic volume reduction during exercise could be explained by impairment of myocardial contractility. The inability of the LV to further augment stroke volume beyond light-intensity exercise is likely a reflection of occult left ventricular dysfunction and poorer response in terms of myocardial contractility. With incremental exercise, the continued rise in cardiac output is therefore best explained by the rise in HR. The volumetric findings during light-intensity exercise concur with Tischler et al (273) in that in patients with asymptomatic severe MR and normal LV ejection fraction at rest, there is an improvement in LV ejection fraction and an increase in forward stroke volume during exercise(273). As this study had only assessed 2 stages of exercise (light and moderate-intensity), it is therefore worth noting that our data would not have captured the changes seen during peak-intensity exercise.

In the RV, pressure overload due to development of pulmonary hypertension could have resulted in little change in its end-diastolic volume. The contractility of the RV appeared to improve at higher-intensity of exercise resulting in a smaller end-systolic volume than at baseline. Additionally, RV cardiac output and RV cardiac index were observed to increase significantly during light-intensity exercise and appeared to plateau with further exertion. The largest exercise echocardiography study (n=196) performed by Kusunose et al (70) in patients with asymptomatic degenerative MR showed that exercise-induced RV dysfunction portends worse prognosis. Similarly, assessment of RV function during exercise using radionuclide cineangiography in asymptomatic patients with normal biventricular function at rest, has been shown to predict subsequent development of surgical indications in patients with a decrease in RV ejection

fraction during exercise(274). In our study, only 1 patient had a marginal drop in RV ejection fraction during moderate intensity exercise.

6.5.4 Assessment of MR severity

In this study, we employed two methods in the assessment of MR severity. The indirect method (comparing LV stroke volume with aortic forward flow) for quantitation of MR is highly reproducible and considered robust, as it is not affected by the direction or eccentricity of the regurgitant jet, nor affected by the presence of aortic regurgitation and it makes no haemodynamic or LV geometry assumptions, as is often the case in echocardiography(115,129,142). Assessment of MR volume was also performed using the volumetric technique, which involves the subtraction of the RV stroke volume from LV stroke volume. The MR volume derived from the volumetric method was significantly lower than by the flow method even at rest and did not correlate with MR severity from echocardiographic evaluation and is unlikely to be reliable. This could be explained by classical technical pitfalls and limitations of the volumetric method. This method is much more prone to error and fails in the context of multiple valvular lesions(113), particularly in the context of tricuspid regurgitation. The calculation of the RV stroke volume is also less reproducible in the short axis stack (compared to a trans-axial stack) and the presence of extensive trabeculation in the RV leads to challenging identification of endocardial borders for the purpose of analysis. MR volume (flow method) correlated very well with MR fraction (flow method) ($r^2 = 0.96$) and was therefore used as a reference point in this study to indicate MR severity, justifications as previously outlined in the results section. Furthermore, MR $volume_{flow}$ correlates very well with MR $fraction_{flow}$ ($r=0.97$, $p<0.001$) during rest and exercise, confirming the reliability of the flow method in MR quantitation.

6.5.5 Exercise-induced changes in MR severity

The results of the present study show that, as in functional MR(264), degenerative MR can have a dynamic component with marked exercise-induced changes. Data supporting exercise-induced changes in echocardiographic parameters to quantify MR are limited(88,89,275). Only an exercise-induced

increase of the EROA by ≥13 mm^2 has shown to be associated with a significant increase in relative risk of death and hospitalisation for cardiac decompensation in functional MR(276). Unfortunately, EROA is difficult to measure, especially during exercise when imaging window is suboptimal. Doppler methods used to quantify MR also have further pitfalls(58). Furthermore, the PISA method is limited as its measurement of PISA radius is only taken at one velocity and time point. The change in PISA throughout the systole cycle therefore makes quantitation of MR severity challenging with echocardiography(58). There are also other factors which can play a role in the dynamic changes of MR during exercise, e.g. alterations of pulmonary resistance and neuro-hormonal activation(275).

Under resting conditions, MR volume is determined by the EROA, the systolic atrioventricular pressure gradient, the forward: reverse impedance ratio, and the duration of systole(277). During exercise, the increase in myocardial contractility allows the LV to adequately adapt forward stroke volume and cardiac output to central and peripheral demands.(71). The systolic pressure gradient increases, the duration of systole decreases, and regurgitant volume depends mainly on the size of the EROA. There are several theories to account for the variable change in MR during exercise. Firstly, in degenerative MR (i.e. mitral prolapse or flail), the decrease in LV cavity volume during exercise could possibly contribute to the increase in MR by increasing the extent of the leaflet prolapse. Secondly, geometric changes associated with the LV size during exercise can also induce a stretching of the leaflets more widely over the annulus, resulting in increased MR. Thirdly, progressive dilatation of the MV annulus during exercise might also affect leaflet coaptation and worsen MR by increasing systolic mitral valvular tenting, as suggested in some studies (89,270). In the context of exercise, despite the increase of EROA in these scenarios, the shortened systolic phase due to the rise in HR may reduce the time through the EROA and may therefore compensate for the degree of MR, resulting in little overall change in total MR volume per cardiac cycle. Conversely, patients with no change or decrease in MR severity during exercise may have had no significant change in mitral annulus area. The reorganisation of leaflet closing forces during exercise could also modify the leaflet prolapse configuration, improve coaptation, and lead to a

reduction in MR volume. Finally, the severity of MR may increase in some patients and decrease in others without a clear pathophysiological mechanism.

Few echocardiographic studies have demonstrated that MR severity can be dynamic during exercise(89,272,273,278). Our findings were quite similar to Leung et al (278), where a third of patients with MR secondary to MV prolapse had significant increases in MR volume during exercise. The recent study by Bakkestrøm et al (272) also found that MR was associated with a more unpredictable response to exercise, especially in asymptomatic subjects. This is likely due to the ability of the LV and LA to accommodate increases in venous return from the periphery with exercise, particularly when LV compliance is normal. The different responses to exercise could be reflected in the variable changes in MR volume in individual patients. This would also be in agreement with the findings by Magne et al(89), where degenerative MR (due to MV prolapse) was dynamic and markedly increased during exercise in one-third (32%) of patients, markedly decreased in 26% of patients, and remained relatively unchanged in 42% of patients. In addition, the location of prolapsed leaflet (anterior versus posterior), and especially the presence or absence of flail leaflet, was also associated with diverse responses to exercise(89). Magne et al(89) also demonstrated that patients with a marked increase in MR volume (>=15mls) during exercise had lower symptom-free survival than those in whom MR decreased or remained unchanged ($p = 0.0015$). In our highly selected patient population, only 1 patient had an increase in MR volume of more than 15ml. It is therefore not possible to adequately stratify the patients into the MR improvers or MR worsening group.

6.5.6 Pathophysiology of MR at rest and during exercise

MR is a condition of volume overloading which results in eccentric hypertrophy and an increase in LV mass and end-diastolic volume (279). The increase in EDV allows augmentation of total stroke volume, while maintaining forward stroke volume near normal. In chronic MR, afterload is normal due to compensatory increase in wall thickness(279). Ejection fraction is preserved due to the low impedance of the outflow circuit into the LA; even after contractile function has

been impaired(280). Both MR volume and MR fraction depend on EROA, duration of MR during systole, the systolic atrioventricular pressure gradient and the forward: reverse impedance ratio. The severity of regurgitation and the effect on ventricular function vary also with loading. LV dysfunction often only truly manifests itself after corrective surgery and has been shown to be strongly predictive of poor long-term survival(281,282). Surgical intervention before any irreversible decline in contractile function has occurred is therefore desirable. The hemodynamic response to exercise in MR relies on the change in the severity of the regurgitant lesion and the ability of the LV to meet increases in demands on workload. These two factors interact in complex ways.

6.5.6.1 Change in severity of regurgitation lesion

The severity of MR can be assessed in terms of various parameters that vary in their response to exercise (EROA, MR volume, MR fraction). Some studies have suggested that in patients with normal LV function, such as in this study, MR volume and EROA may decrease (or increase in some cases of MV prolapse) (279). In exercising healthy ventricles, MR fraction may appear to decrease as stroke volume increases during exercise. The fall in EROA and systemic vascular resistance both reduce the MR volume and MR fraction. In cases of MV prolapse, the effect of increase in EROA can be offset by a reduction in systemic vascular resistance (forward impedance) and helps explain why MR volume and MR fraction in this condition will usually decrease with exercise(87,273,278). In those with impaired LV function, even though EROA may increase, the impaired myocardial contractility to drive MR into the LA may result in no overall change in MR volume. As both MR volume and SV remained low, this can lead to no change in MR fraction. In flail leaflets and rheumatic disease, EROA is relatively fixed throughout systole (283). In these instances, EROA will not be expected to change much when LV function is normal but might increase due to annular dilatation when LV function becomes impaired. The increase in ESV during exercise can also further increase EROA. EROA can however be dynamic and vary with ESV in those with MV prolapse. Paradoxically, in MV prolapse, patients with normal LV function may have an increase in EROA on exercise because reduction in ESV causes more marked mitral prolapse(270,284). In ischemic MR,

EROA and severity of MR will however depend on the level of ischemia induced and on the response of ESV to exercise(279).

6.5.6.2 Response of LV function to exercise in MR

In asymptomatic patients with a normal resting LV ejection fraction, the response of LV volume to exercise is the same as that of normal subjects with little change in EDV, a decrease in ESV, and increases in LV ejection fraction and forward stroke volume (with no change or a small increase in total stroke volume)(87,273,278,284). In supine bike-exercise echocardiographic studies of asymptomatic patients, little or no change in LV ejection fraction with exercise was found (281,285). These studies stipulated that lying supine increases preload, so that exercise causes little further change in stroke volume and end-diastolic volume (286). In addition, patients with significant MR already have greater than normal preload and the effect of lying supine is assumed to place them on the flat portion of the Starling curve. Thus, any further increase in preload with exercise does not augment systolic function. This may explain the findings in our study where the increase in ejection fraction and stroke volume plateaued when patients were subjected to increasing exercise workload. Symptomatic individuals with normal or lower than normal resting LV ejection fractions have abnormal responses to supine exercise and exhibit no change in ejection fraction, EDV, and ESV (281,287). LV ejection fraction may even decline in some (288). In advanced cases of heart failure with significant MR, the LV volumes, ejection fraction and, forward and total stroke volumes were not changed by upright exercise(289).

6.5.7 Predictors of MR severity

In this study, we found that a higher degree of MR at rest and during exercise were associated with a larger ventricle (LV end diastole and systole) and higher stroke volume. A larger LV end-diastolic volume was a predictor of a higher MR volume at rest whilst LV stroke volume (r^2=0.88, p=0.001) was found to be the strongest predictor of MR severity during exercise. In severe MR, the LV adapts by increasing the LV end-diastolic volume in order to accommodate the volume

overload. During exercise, the increase in myocardial contractility also increases the total stroke volume in order to maintain the forward stroke volume.

A lower aortic net flow during exercise and younger age predicted worsening of MR during exercise. When EROA increases during exercise, the reduced atrioventricular resistance results in a larger blood volume ejected into the LA and therefore resulting in a smaller blood volume through the aortic valve equating to a lower aortic net flow. Younger age patients could have a relatively better myocardial contractility during exercise, and the maintained afterload could be the driving force of MR into the LA. Despite this, it is possible that the LA is highly compliant at these ages to accommodate the higher MR volume and therefore did not result in pulmonary hypertension or manifestations of symptoms.

Similar to other studies looking at chronic secondary/ischaemic MR (264), we found that resting MR severity cannot predict the magnitude of exercise-induced increase of MR. The change in LV end-systolic volume, LV stroke volume and ejection fraction during exercise were also not associated with exercise-induced change in MR severity. In addition, poorer augmentation of LV ejection fraction was not associated with worsening of MR severity during exercise. When MR severity increases, aortic net volume was seen to decrease significantly. Although some studies found that a smaller ESV could result in worse coaptation between the valves and thus worsen the degree of prolapse and increase MR volume, we did not find such association. Our findings are consistent with those found by Magne et al(89), where although EROA significantly increased during exercise with both methods (PISA and Doppler), there were no significant exercise-induced changes in the overall regurgitant volume. In the context of exercise, the increase in EROA could possibly be offset by the increase in HR which shortened time in systole. Interestingly, even though some studies have suggested that systolic BP during exercise in the patients who developed worsening MR was higher than that in those who did not (due to higher driving pressure), we did not find such association.

6.5.8 Comparison with healthy volunteers

In healthy volunteers as described in the previous chapter, LVEDV decreased significantly during moderate and high-intensity exercise. In contrast, patients with significant MR had unchanged LVEDV throughout exercise. It is likely that the decrease in LVEDV in patients were hampered due to the already increased in ventricular volume overload due to the MR. Similarly, although healthy volunteers sustained a significant decrease in RVEDV during high-intensity exercise, this was not observed in the patient group. An increase in MR volume or pulmonary pressures could have impaired the reduction of RV end-diastolic volume (i.e. contractility performance) during exercise. In healthy volunteers, LVESV was only significantly lower during moderate exercise. However, this was not observed in the patient group. It is likely that the patients were not exercised sufficiently for this to be observed, although the likelihood of an impaired LV contraction during exercise remains a possibility. Similar to healthy volunteers, RV end-systolic volume significantly decreased during high-intensity exercise compared to baseline.

Unlike healthy volunteers where LV stroke volume remained unchanged, patients with significant MR increased their stroke volume during light intensity exercise. This can be explained by compensatory mechanism of the LV to increase aortic forward flow due to the increased mitral regurgitant volume into the LA. RV stroke volumes were similar to healthy volunteers as they remained unchanged. Unlike healthy volunteers where ejection fraction for both ventricles were significantly higher during high-intensity exercise when compared to their respective baseline values, patients augmented their ejection fraction only during light intensity exercise and ejection fraction appeared to plateau thereafter (LVEF 58±3% vs 64±4% vs 64±4%; baseline vs light vs moderate; p=0.003 vs 1.000 vs 0.007 and RVEF 52±4% vs 56±8% vs 60±5%; baseline vs light vs moderate; p=0.16 vs 0.43 vs 0.002). In severe MR, progressive increase in LV and LA pressure also leads to a backward passive rise in the pulmonary vein pressure and post-capillary pulmonary hypertension which often results in dyspnoea. The failure of the RV to augment ejection fraction during exercise could be due to an increased pulmonary pressure (after-load resistance). During exercise, LV and RV cardiac indexes also increased during initial stages of exercise and then plateaued

thereafter in contrast to that seen in the healthy volunteers where cardiac indexes continued to rise.

The differences between our study and findings of other exercise echocardiography studies may be explained by differences in exercise protocol, body posture (left lateral decubitus, semi-supine, supine) and aetiology of MR studied (239). Methodologic limitations due to different imaging modalities may also account for the lack of consistency in previous studies. Although our study was limited to significant degenerative MR, some echocardiographic studies have included a wider range of MR aetiologies in their tested population (i.e. rheumatic, ischemic) and also included those in the mild-moderate range of MR (8). These factors could have resulted in varying response of MR with exercise.

6.5.9 Impact on practice

This small patient series suggests clinical feasibility of using navigated exCMR for the assessment of cardiovascular response during continuous exercise in patients with significant mitral regurgitation. Larger prospective studies are needed to further evaluate the prognostic value of the data acquired, including its impact on clinical management decisions.

6.6 LIMITATIONS

The unique characteristics of this cohort limited the sample size, and the findings should therefore be interpreted with caution. Nevertheless, to date, this is the first study to assess feasibility of navigated exCMR in a challenging group of patients with significant valvular heart disease, and therefore offering insights into their exercise metrics. All patients included in this study presented with degenerative MR due to mitral valve prolapse and were in sinus rhythm. The findings can therefore neither be applied to patients with other organic MR aetiologies, such as rheumatic valve disease or endocarditis nor can the results be extrapolated to patients with atrial fibrillation. Patients with pulmonary congestion or unstable

haemodynamics were excluded, and these data should only be extended to stable ambulatory patients. Cycling whilst lying in a flat, supine position is an unorthodox form of exercise, and skeletal muscle fatigue may lead to premature test termination(239). This exCMR protocol is therefore not suitable for those unable to exercise due to orthopaedic problems or poor conditioning. Hence, this may introduce selection bias by excluding more sedentary patients. Knee-to-bore clearance whilst cycling is also limited by patient height and magnet bore diameter.

Acclimatisation of the body to a supine position could have resulted in haemodynamic changes which can influence the degree of MR. This can therefore lead to uncertainty in the real variation in MR during different stages of exercise. It was also not possible to exclude the possibility that the changes in MR severity was due to chance observations as a result of scan-rescan variation. There is currently no known clinical trials which has assessed the minimum exercise-induced change in MR severity (quantitatively) which has had significant prognostic implications.

The inclusion criteria were dependant on the initial quantitation of MR with echocardiography and the classifications of MR may not be accurate, especially in the setting of eccentric, non-holosystolic (i.e. late systolic) doppler envelope as often seen in MV prolapse. As the echocardiographic studies were acquired for clinical purposes, and it is possible that they were not as comprehensive as those performed specifically for a research study. This may have led to a wider range of MR severity seen in these patients when assessed by CMR criteria.

As it was not feasible for patients to breath-hold immediately post-cessation of exercise and in order to reduce the degree of through-plane motion, PC aortic flow imaging was performed during free-breathing recovery phase. This is supported by previous work demonstrating that the choice of pulse sequence (free breathing versus breath hold) does not significantly affect the quantitative results(215). The drop in HR following cessation of exercise could nevertheless have influenced the accuracy of aortic flow measurements, and therefore MR

quantitation; although this limitation applies also to current echocardiographic modalities.

In addition, inherent limitations of PC imaging (including phase offset, suboptimal selection of velocity-encoding gradients during acquisition, and reliance on image plane selection) can interfere with optimal quantification of aortic flow. Measurement of aortic flow at the sino-tubular junction (instead of at the level of the valve) might also underestimate the aortic flow by 10% to 15%(220), and thus cause modest overestimation of the MR. However, quantitation of MR severity by CMR is generally associated with high accuracy and reproducibility(114,221).

CMR currently has little means of testing intracardiac pressure, one entity which determines referral for surgery. An increase in MR volume during dynamic exercise has been shown to correlate well with elevation of systolic pulmonary artery pressure (275), suggesting that this can be used as a surrogate marker. Because no follow-up or outcomes are provided, we do not know whether asymptomatic patients with abnormal response to exercise are indeed at higher risk and in (earlier) need for intervention.

6.7 CONCLUSION

The navigated exCMR protocol is feasible in clinical patients and allows simultaneous assessment of the left and right ventricular response to *continuous* exercise. Primary MR appears to be a dynamic entity in this small study although there remains uncertainty about how MR changes during exercise. Clinical feasibility of this protocol suggests a future role for larger clinical trials in the assessment of patients with exercise-related symptoms.

Chapter 7 OVERALL DISCUSSION

The assessment of MR with echocardiography can be challenging in the context of non-holosystolic, eccentric jets and can often be limited by body habitus. Accurate assessment of MR severity and its complications are important, as it not only determines timing and indication for surgical correction, but also carries significant prognostic implications. As non-invasive cardiovascular imaging improves and evolves, CMR imaging has been shown to be the reference standard for ventricular volumes assessment and has allowed insights to be gained into a more precise quantitative measure of MR severity and its associated adverse cardiac parameters(112,114,121).

The overarching aim of this thesis was to explore the utility of both existing and emerging CMR imaging techniques in the assessment of MR, whilst applying the concept to a variety of clinical settings. Chapter 3 evaluated the change in MR severity and its associated mortality outcome in patients undergoing TAVI, whilst Chapter 4 assessed the relative impact of two different strategies of MV surgery (repair versus replacement) on cardiac reverse remodelling parameters. Patients with MR can often have exertional symptoms and physiological exercise testing can help detect underlying cardiovascular abnormalities which are not apparent at rest. Hence, Chapter 5 investigated the new application of the navigated pulse sequence technique for biventricular physiological assessment during continuous physical exercise. Its subsequent translation into clinical practice (i.e. patients with severe MR) was subsequently assessed in Chapter 6.

Current literature reporting the impact of concomitant MR on outcome in patients who undergo TAVI are conflicting and are mainly based on echocardiographic data; which can be limited by poor acoustic windows, eccentric jets and geometric assumptions (140). Chapter 3 describes the first CMR study to specifically assess MR in quantitative terms and evaluate its impact on cardiac reverse remodelling and mortality in patients undergoing TAVI. In high risk patients with severe aortic

stenosis, the presence of MR may influence the management decision (medical, TAVI or surgical option). This longitudinal follow up study has demonstrated that MR is likely to improve following TAVI without the need for any specific intervention on the mitral valve. Furthermore, the absence of MR improvement was not associated with any adverse impact on cardiac reverse remodelling. More importantly, significant MR at baseline was not associated with reduced survival.

Mitral valve (MV) repair is currently recommended over replacement. The guidelines suggesting this are however based on historic evidence which compared outdated techniques of MV replacement. Recent data have casted doubts on its validity in the current era of chordal-preservation techniques in MV replacement. Chapter 4 found that MV surgery, on the whole, led to a positive left atrial and left ventricular reverse remodelling. Contrary to old literature, MV replacement with chordal preservation appeared to have similar postoperative cardiac remodelling as MV repair in this small pilot study. Although decline in global LV ejection fraction was frequently seen following MV surgery, this was similar across both repair and replacement groups. In this small patient series, residual MR following MV repair did not appear to lead to a less favourable cardiac reverse remodelling. If these findings are indeed valid, this could potentially be the first step towards allowing guidelines, which currently favour the repair strategy, to be more flexible. This could therefore indicate that in those with more complex mitral valve disease which is possible but difficult to repair, a mitral valve replacement may be considered an acceptable option.

Current CMR image acquisition techniques during exercise typically require either transient cessation of exercise or complex post-processing analysis, potentially compromising their clinical utility. Chapter 5 demonstrated the feasibility of the free-breathing, multi-shot, navigated image acquisition method in the serial assessment of biventricular response to *continuous* exercise. With this technique, intra- and inter-observer readings were highly reproducible. A further advantage is that image analysis can be performed on commercially available software, a limitation of current available techniques. The clinical translation of this navigated image acquisition techniques during exercise was

tested in Chapter 6 in clinical patients with significant MR. This small study found that navigated exCMR protocol was feasible in clinical patients with significant mitral regurgitation. The change in MR during exercise was also found to be variable in individual patients. There remains uncertainty however about how MR changes during exercise and it was not possible to exclude MR variability due to scan-rescan variation.

Both Chapters 5 and 6 have demonstrated that navigated exCMR technique allowed simultaneous assessment of left and right ventricular response during *continuous* physical exercise and was found to be feasible in both healthy volunteers and clinical patients. This has highlighted the potential of using ‘navigated’ exCMR in larger clinical trials for the assessment of cardiovascular response during continuous exercise.

Chapter 8 CONCLUSION

As each imaging modality has its intrinsic advantages and limitations, an integrated multimodality imaging approach is essential for a comprehensive assessment of MR. Although echocardiography is widely accessible and offers excellent morphological and functional information, it is limited by its suboptimal reproducibility in severity assessment. CMR is highly accurate in the quantitation of MR severity and should be considered as an alternative modality in those with eccentric MR or suboptimal echocardiographic images. With the use of a more precise and reproducible CMR imaging method, this body of work is deemed to have contributed positively to the current available literature.

Although significant MR is common in patients undergoing TAVI, it is likely to improve following TAVI without the need for any intervention on the mitral valve. Improvement in MR in the TAVI population was also not associated with LV reverse remodelling. More importantly, significant MR at baseline was not associated with reduced survival.

MV surgery leads to positive left atrial and left ventricular reverse remodelling. A decline in global LV ejection fraction is a common post-operative finding. MV replacement with chordal preservation techniques appears to have similar cardiac reverse remodelling benefits to MV repair in this small pilot study. Although residual MR is often seen following repair, this did not lead to a less favourable cardiac reverse remodelling. Larger clinical studies are required to support and validate these findings before clinical practice can be influenced.

ExCMR has the potential of providing quantitative cardiac indices; whilst offering a direct link between physical activity, symptoms and stress imaging findings. Additionally, it can offer important information such as functional capacity, BP response and developments of arrhythmias. The navigated exCMR protocol

allows assessment of cardiovascular response during continuous exercise. Intra and inter-observer readings were highly reproducible. The clinical feasibility of navigated exCMR was demonstrated in a small group of clinical patients with significant MR. Although primary MR was found to be a dynamic entity in this study, there remains uncertainty about exercise-induced changes in MR and it was not possible to exclude MR changes due to scan-rescan variation. The feasibility of this protocol in both healthy volunteers and clinical patients with MR suggests that larger clinical trials with expanded sample size are required to evaluate its future role in the assessment of patients with exercise-related symptoms.

8.1 FUTURE DIRECTIONS

Three-dimensional (3D) cine (time-resolved) phase-contrast CMR with three-directional velocity-encoding (‘4D flow CMR’) allows correction for MV motion and is now a developing technique which allows quantification of flow within the entire heart in all directions(141). This highlights the potential for comprehensive MR flow data to be obtained in the near future. In patients undergoing TAVI, the prognostic value of significant MR according to its aetiology (organic vs functional) is one to be addressed in future prospective studies. It would also be useful to elucidate if amelioration of MR following TAVI would persists at a much longer term follow up (1-2 years).

Larger scale, prospective clinical trials are required to validate the findings in Chapter 4 before clinical decisions can be made based on CMR parameters. Utilising the tissue characterisation strength of CMR, future studies can also focus on investigating the impact of fibrosis (late gadolinium enhancement) on cardiac reverse remodelling and mortality outcomes in patients undergoing MV repair and MV replacement.

Although the findings in Chapter 6 are promising, larger scale clinical trials are necessary to investigate the value of exCMR in influencing the management of

MR. Further studies should also examine if the use of exCMR can truly help risk stratify asymptomatic patients with severe MR through the assessment of exercise-induced LV and RV dysfunction, or the change in MR severity. Follow-up of these group of patients for mortality outcome data would further strengthen the value of assessing exercise-induced changes. Furthermore, a baseline CMR study investigating the scan-rescan MR variation would be important to understand the expected MR variation on a supine exCMR study. Being able to identify the minimum change required in exercise-induced MR severity, if found to have prognostic implications, may also help risk stratify patients. In addition, the use of exCMR can create new avenues for research and clinical practice, such as stress evaluation of ventricular dysfunction. This is particularly relevant to pathologies of the LV and RV, and pulmonary circulation that are challenging to assess by other imaging modalities. Future work can also look into assessing the accuracy of this exercise imaging method in deriving cardiac output against invasive exercise standards (direct Fick method). Further assessment of this exCMR protocol in larger clinical trials is now warranted for assessment of cardiac pathologies where current exercise imaging modalities have been shown to have limitations.

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APPENDIX

Ethical approval letters and consent form for Chapter 3

NHS
Health Research Authority

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

Tel: 0113 30 50116
Fax:

19 December 2012

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

Dear Dr Greenwood

Study title:	**MRI Evaluation of Transcatheter and Surgical Aortic Valve Implantation.**
REC reference:	**08/H1307/106**
Amendment number:	**Four.**
Amendment date:	**30 November 2012**
IRAS project ID:	**6033**

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

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
PIS and consent	1.3	30 November 2012
Protocol	1.4	30 November 2012
Notice of Substantial Amendment (non-CTIMPs)	Four.	30 November 2012

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

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 NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

08/H1307/106:	**Please quote this number on all correspondence**

Yours sincerely

p.p. 

Dr Rhona Bratt
Chair

E-mail: marcneal@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*
Ms Clare Skinner

Leeds Institute of Cardiovascular and Metabolic Medicine

Division of Cardiovascular and Diabetes Research
Sunshine Corridor
Leeds General Infirmary
Great George Street
Leeds, LS1 3EX

UNIVERSITY OF LEEDS

MRI evaluation of Transcatheter and Surgical Aortic Valve Implantation

Patient information Leaflet

Version 1.3 November 30 2012

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 are scheduled by their consultant for replacement of their aortic valve. We are looking at two groups of patients in this study: patients who are going to have a surgical valve replacement (done by a heart surgeon), and 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.
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 the decision of how your valve is going to be replaced.

WHAT IS THE PURPOSE OF THE STUDY?

Patients have their aortic valve replaced 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 two groups of patients.
We 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 want to 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?

It is 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?

All patients in this study will have MRI scans of their head and heart before and after the valve replacement procedure. Before the valve replacement we will scan your head and heart during one visit to the MRI department, this visit can take place before your admission, or whilst you are already an in-patient in the hospital. This scan will take approximately 60 minutes to complete. After the valve replacement, and before you go home, if you have had a surgical valve replacement (AVR) we will scan your head only, which takes about 10 minutes. If you have had a transcatheter replacement (TAVI), we would like to scan your head (10 minutes) and do a shortened version of the heart scan (15 minutes). Approximately 4-6 months later we will ask you to return to the MRI department so we can scan you heart and your head, which takes about 60 minutes. The reason why we want to do this scan later is that your heart's function may continue to improve for some time after the valve replacement.

During each scan 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

As part of the study we will ask you to fill out 2 questionnaires which will ask questions about how you feel the quality of your life is. A member of the research team can help you with this if you need assistance. We will ask you to complete these again after 1 month, 6 months, and 1 year. At the same time points we will also ask you to do a number of tests which look at memory and other functions of the brain. These tests will take about an hour on each occasion. If you feel too tired or unwell to come to the hospital we may ask if we can visit you in your own home to do these tests.

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. 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.

BENEFITS TO YOU
There are no particular benefits to you from taking part in this study.

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, which is collected about you during the course of the research will be kept strictly confidential. This information will be securely stored at the Cardiac MRI Unit at Leeds General Infirmary on paper and electronically, under the provisions of the 1998 Data Protection Act. You will not be identified in any publication that may result from this research. All data will be anonymised so that your identity will not be revealed to anybody outside the Cardiac MRI Unit at Leeds General Infirmary.

With your permission, we will inform your General Practitioner (GP) of your participation in this study as well as in the event of an unexpected abnormality on the scan.

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

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

If you have a private medical insurance please ensure that participation in the study does not affect your cover.

WHO IS ORGANISING AND FUNDING THE STUDY?
This is a research project of the Cardiac MRI department at Leeds General Infirmary.

WHO HAS REVIEWED THE STUDY?
The study has been reviewed and approved by the Leeds West Local Research Ethics Committee.

For further information please contact:

Ms Fiona Richards / Ms Petra Bijsterveld
Cardiovascular Research
Leeds General Infirmary
LS1 3EX
Tel: 0113 392 5224 / 0113 392 5481

or

Drs TA Musa / LE Dobson
Cardiac MRI Department,
B Floor, Clarendon Wing,
Leeds General Infirmary,
LS1 3EX

cmrresearch@leeds.ac.uk

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

Hospital Number: …….. Initials: ……..

CONSENT FORM – Version 1.3 November 30 2012
MRI evaluation of Transcatheter and Surgical Aortic Valve Implantation

	Name of Researcher: Prof John Greenwood	Please initial box
1.	I confirm that I have read and understood the information sheet (version 1.3 November 30 2012) for the above study and have had the opportunity to ask 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.	☐
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	☐
5.	I understand that my participation is voluntary; and that I am free to withdraw at anytime, 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.	If I were to lose capacity, I understand that data already collected will be kept and used for the purposes of the study.	☐

Signature.....

Name (block capitals).....Date…….

Signature of witness.....

Name (block capitals).....Date…….

Ethical approval letters and consent form for Chapter 4

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

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 (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 – a pilot study'

Patient information Leaflet

Version 2.2 September 21 2017

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 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 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.

We 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?

All patients 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. 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).

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. 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 Leeds Teaching Hospitals NHS Trust and University of Leeds secure servers, and on paper, under the provisions of the 1998 Data Protection Act. You will not be identified in any publication that may result from this research. The data collected will be coded and your personal details will be kept entirely separately from details about your health and treatment. You will not be identified in any publication that may result from this research.

With your permission, we will inform your General Practitioner (GP) of your participation in this study.

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

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.

If you have a private medical insurance please ensure that participation in the study does not affect your cover.

WHO IS ORGANISING AND FUNDING THE STUDY?

This study is being organised by the Leeds Institute of Cardiovascular and Metabolic Medicine (LICAMM) within the University of Leeds.

WHO HAS REVIEWED THE STUDY?

The study has been reviewed and approved by an approved Research Ethics Committee.

For further information please contact:

Ms Fiona Richards / Ms Petra Bijsterveld
Cardiovascular Research
Leeds General Infirmary
LS1 3EX
Tel: 0113 392 5224 / 0113 392 5481
cmrresearch@leeds.ac.uk

or

Dr Peggy Chew
Cardiac MRI Department,
B Floor, Clarendon Wing,
Leeds General Infirmary,
LS1 3EX

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

Hospital Number: …… Initials: ……..

CONSENT FORM – Version 2.2 September 21 2017– MRI-MVR

	CI: Prof John Greenwood	Please initial box
1.	I confirm that I have read and understood the information sheet (version 2.2 September 21 2017) 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:

Ethical approval letters and consent forms for Chapters 5 and 6

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

Telephone: 0113 3050122
Facsimile: 0113 8556191

24 January 2013

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

Dear Dr Greenwood

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

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

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

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

Confirmation of ethical opinion

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

Ethical review of research sites

NHS sites

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

Non-NHS sites

Conditions of the favourable opinion

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

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

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

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

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

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

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

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

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

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

Approved documents

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

Document	*Version*	*Date*

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

Statement of compliance

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

After ethical review

Reporting requirements

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

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

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

Feedback

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

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

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

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

The Leeds Teaching Hospitals NHS
NHS Trust

UNIVERSITY OF LEEDS

VOLUNTEER INFORMATION SHEET
Version 1.2 August 4th 2016

CE-MARC 2: Optimization of acquisition and analysis methods (healthy volunteers).

Chief Investigator: Professor John Greenwood

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. With Cardiac MRI we are able to detect a number of important abnormalities that are caused by heart disease. Importantly, MRI is a safe test and does not use any radiation. MRI may become one of the most important tests in patients who suffer with different types of heart disease.
We have been doing MRI scans of the heart in Leeds since 1995. However, research into improving the images is a continuous process. We always work at developing and improving the scanning protocols, i.e. the computer programmes that produce the images of patients' hearts.

Why have I been chosen?

This study is looking at up to 300 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. 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 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 minutes to complete. You lie in a short 'tunnel', which holds a large magnet. Short bursts of radio waves from the MRI scanner allow images to be created. You will hear periodical loud "banging" noises while we are acquiring the images of your heart, so we protect your ears with headphones through which you can listen to the radio or one of your own CDs. We will remain in communication with you throughout the scan. For

most scans we will insert one or two cannulae (small plastic tubes) into veins in your arm. It is likely that we will inject a contrast dye during the scan. Usually people are not aware of the contrast dye injection. At one point we may also inject a medication (Adenosine) into a vein in your arm, which is a drug to increase the blood flow to your heart. This can cause a brief feeling of warmth, breathlessness or chest discomfort. However all of these feelings, if they occur, usually settle within one or two minutes. A doctor will stay in the room with you whilst you are having the medication. In some cases instead of using adenosine we may immerse your hands or feet in cold water for up to 2 minutes to achieve the same increased blood flow to the heart muscle, or we may ask you to use a cycle ergometer, a bicycle which can be used whilst lying down in the scanner.
If we wish to obtain specific images of your heart arteries we will wrap a belt around your abdomen to help improve the quality of the pictures. This is not painful and is a recognized method of doing this type of scan. You may be given a nitrate (GTN) spray under the tongue which helps us to obtaining good images. If your heart beat is quite fast we would give you a beta blocker to reduce your heart rate. Again, these methods are widely used in other centres worldwide and are used in normal clinical work too.
Some of the MRI methods used in the heart are also applicable to other body organs. In some patients we will, for example, take images of the blood vessels and/or muscles in the abdomen, or a leg or arm during the same scan. The only difference to the heart scans is that we will use a different receiver coil (the aerial used for reception of MRI signals) to obtain these images.
As this study is about improving our scan protocols on an ongoing basis for a period of five years the information we give you has to describe all the different techniques we wish to use in the study overall, but not all the techniques described above will be used during your scan(s). Before you sign the consent form we will discuss with you the specific scanning protocol that we are going to use.

We may ask you for a blood sample, which would be taken whilst we insert the cannula in your arm for the contrast, so there are no extra needles involved. Knowing your haematocrit (the volume percentage of red blood cells in the blood) helps us to create specific images which are applicable to clinical practice. We may also test your blood glucose level. In the unlikely event of an 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. 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 at Leeds General Infirmary on paper and electronically, under the provisions of the 1998 Data Protection Act. You will not be identified in any publication that may result from this research.

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

With your permission, your data may also provide a resource for future studies. If any information from this study is used to develop new research, data protection regulations will be observed and strict confidentiality maintained. Ethical approval will be obtained for any future studies involving your data. You will not be identified in the results of any future studies.

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

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

The research organisation
This is a research project of the Cardiac MRI department at Leeds General Infirmary.

For further information please contact:
Petra Bijsterveld
Research Nurse
CMR Clinical Research Group
X47 Sunshine Corridor
Leeds General Infirmary
Leeds
LS1 3EX
T 0113 392 5481
F 0113 392 5225
M 07922 512 887
Email p.bijsterveld@leeds.ac.uk

CONSENT FORM v 1.2 August 4th 2016

CE-MARC 2: Optimization of acquisition and analysis methods (healthy volunteers).
Chief Investigator: Professor John Greenwood

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

Name ……

Please initial boxes

1. I have read the Volunteer Information Sheet dated August 4th 2016 (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 a computer system, and, after my personal details have been removed, may be available to researchers at other institutions. ☐
6. I understand that some of the blood samples taken from me may be stored and may be analyzed in the future for markers related to heart disease ☐
7. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from the University of Leeds, from regulatory authorities, or from the Leeds Teaching Hospitals NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐
8. If I were to lose capacity, I understand that data already collected will be kept and used for the purposes of the study. ☐
9. I agree to take part in this research study and that the general results of the study will be made available to the medical community most likely through publication in a reputable medical journal. ☐

Signature.....

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

Signature of researcher.....

Name (block capitals).....Date……