Cardiovascular Magnetic Resonance Imaging in Mitral Regurgitation

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Intellectual Property and Publication Statements

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

Chapter 1

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Authorship: MG was responsible for the 4DF data analysis, statistical analysis, literature review and write up of the draft manuscript. MG, TPC, PGC, LED, LAEB were

responsible for patient recruitment, patient consent, CMR acquisition and CMR analysis. CC was responsible for performing TTEs and the majority of TTE analysis. MMB was responsible for providing 4DF expertise and reviewing and correcting all 4DF analyses. MFP helped with TTE analysis. DMH was responsible for oversight of scan protocol and provided 4DF expertise from physics' perspective. ST, NS, WJ, SK, MG, HP and MP helped with patient recruitment and scan supervision. AK provided TTE expertise, reviewed and corrected the manuscript. PPS, SP, EL were responsible for reviewing and correcting the manuscript. PG was responsible for providing 4DF expertise, reviewing and correcting the manuscript. JPG was the principal investigator responsible for the design of the study, oversight of the study and final approval of the submission.

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3) Gorecka M, Nejadhamzeeigilani H, Craven TP, Chew PG, Dobson LE, Brown LAE, Chowdary A, Jex N, Thirunavukarasu S, Sharrack N, Javed W, Kotha S, Giannoudi M, Procter H, Parent M, Swoboda PP, Goddard AJP, Plein S, Level E, Greenwood JP. Silent cerebral infarction and clinical outcomes in surgically treated mitral valve disease. Manuscript under review by JACC-Cardiovascular Imaging.

Abstracts

1) Gorecka M, Nejadhamzeeigilani H, Craven TP, Chew PG, Dobson LE, Brown L, et al. Silent cerebral microinfarction following mitral valve surgery. Heart. 2022;108(Suppl 1):A6-A7.

2) Gorecka M, Nejadhamzeeigilani H, Craven TP, Chew PG, Dobson LE, Brown LAE, et al. Perioperative cerebral microinfarction and quality of life following mitral valve surgery. European Heart Journal. 2022;43(Supplement_2).

3) Gorecka M, Dobson L, Plein S, et al. Two-dimensional and four-dimensional velocity imaging quantified mitral regurgitation is associated with left ventricular remodelling post mitral valve surgery. Heart 2023;109:A199-A200.

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Abstract

Background

Cardiovascular magnetic resonance (CMR) is the reference-standard for biventricular assessment and has potential diagnostic and prognostic advantages in the assessment of primary mitral regurgitation (MR).

Aims

1) To establish whether 4-dimensional flow CMR (4DF-CMR) has associations with post-operative LV reverse remodelling in primary MR.
2) To evaluate feasibility and reproducibility of exercise-CMR in asymptomatic, primary MR.
3) To attempt to develop a clinically applicable pulse sequence for acquisition of 4DF-CMR during continuous exercise.
4) To assess the incidence and characteristics of silent cerebral infarction (SCI) in mitral valve surgery for primary MR.

Methods

1) Forty-four patients with primary MR underwent 4DF-CMR at index assessment. Of those, 29 patients underwent mitral valve surgery and subsequently a follow-up CMR scan at 6-months.
2) Twenty-five asymptomatic patients with primary MR underwent CMR during continuous in-scanner exercise, utilising a free-breathing, respiratory navigated Compressed-SENSE pulse sequence for the acquisition of short-axis cine stack and aortic flow.
3) Ten healthy volunteers underwent 4DF-CMR acquisition during continuous in-scanner exercise. The clinically available 4DF-CMR pulse sequence was optimised during 6 attempts to allow 4DF acquisition in the presence of moderate-intensity heart rate.
4) Seventy-seventy patients underwent cerebral diffusion-weighted MRI (DWI-MRI) at index visit. Of those, 50 patients underwent mitral valve surgery and subsequently a second cerebral MRI scan pre-discharge. SCI was defined as a new high-intensity lesion on the DWI-MRI.

Findings

1) There was a significant association between pre-operative 4DF-CMR-derived MR volume and the post-operative left ventricular remodelling.
2) MR assessment by exercise-CMR is feasible and reproducible.
3) Although a clinically applicable 4DF-CMR pulse sequence during exercise was not fully developed, incremental improvements to pulse sequence were made such that the acquisition was possible during moderate-intensity exercise, with excellent quality images in 1 volunteer.
4) Silent cerebral infarction occurred in a third of patients undergoing mitral valve surgery for primary MR. There were no significant difference between the mitral valve repair and replacement techniques. SCI had no impact on patient quality of life, functional capacity or clinical outcomes.

Table of Contents

List of Tables

List of Figures

Chapter 1
Introduction

1.1 Rationale and Clinical Applications of 4-Dimensional Flow CMR in Assessment of Valvular Heart Disease

1.1.1 Background

Transthoracic echocardiography (TTE) is the first line imaging modality for assessing patients with valvular heart disease (VHD).(1-3) Although it is easily accessible, safe and inexpensive(4-6), it may be limited in cases of poor acoustic windows secondary to large body habitus(7) or in the presence of eccentric(8) or multiple regurgitant jets(9). Echocardiographic assessment of heart valve function can also be challenging due to limited reproducibility(9), operator-dependence(10) and inaccuracy in quantification of regurgitant lesions in certain cases(11). Although transoesophageal echocardiography overcomes some of these limitations and can be performed in patients with suboptimal quality TTE images(1), it can lead to potentially serious complications(12) and increased patient discomfort.

Phase contrast magnetic resonance (PCMR) imaging offers several advantages over echocardiography and can clarify the severity and mechanism of valvular lesions in selected cases.(7, 8, 13) It enables detailed assessment of valvular flow and function with no geometric assumptions, and can therefore accurately assess lesions with multiple regurgitant jets or eccentric jets.(8, 13) Furthermore, assessment of left ventricular (LV) function and remodelling by cardiovascular magnetic resonance (CMR) imaging has been shown to be highly accurate and reproducible.(14) CMR is

also the reference standard for evaluation of right ventricular (RV) morphology and function, and therefore can precisely assess the impact of right-sided valvular lesions on the ventricle.(15) However, despite all of its advantages, PCMR does not allow for accurate direct jet quantification in the atrio-ventricular valves as it does not account for valve plane motion during the cardiac cycle.(13) Also, flow quantification can be significantly affected by phase-offset errors.(7, 16) Furthermore, errors introduced in ventricular stroke volume calculations can lead to inaccurate quantification of atrio-ventricular regurgitant lesions.(6)

Four-dimensional flow CMR (4DF-CMR) is a relatively novel CMR technique, which offers time-resolved 3-dimensional imaging and allows accurate and precise assessment of VHD. It overcomes a lot of the limitations present in echocardiography and PCMR. A typical 4DF whole heart acquisition has a temporal resolution of 30-40ms, spatial resolution of <3mm x 3mm x 3mm and takes 5-10 minutes.(16) Available acceleration techniques, such as kt broad linear speed up technique (*k-t* BLAST) with a 32-channel coil array allow shorter scan times, and make 4DF-CMR more clinically applicable.(17) New acceleration techniques such as prospective undersampling in multiple dimensions (PROUD)(18), k-adaptive-t autocalibrating reconstruction for cartesian sampling (kat-ARC)(19) and *SmartSpeed (*compressed sensitivity encoding featuring artificial intelligence algorithm*)(20)* are emerging and hold promise for an even faster acquisition. Recommended sequence parameters for 4DF imaging are based on the delicate balance between the ideal parameters to provide high quality data and what is clinically feasible in terms of, mainly scan time. The typical sequence parameters are as follows:

field of view, which is sufficient to cover the region of interest; k-space segmentation factor of 2, which reduces scan time, but also decreases accuracy; retrospective ECG gating, which allows coverage of the entire cardiac cycle, but requires complex reconstruction – this is preferred to prospective gating, where the data from end-diastole are not acquired, thus impairing accuracy of mitral valve (MV) and tricuspid valve (TV) forward flow quantification(21); the use of respiratory navigator; elliptical k-space to reduce scan time; flip angle equivalent to at least the Ernst angle to provide optimal signal-to-noise ratio (SNR), but with negative effect on contrast; the use of acceleration techniques, if available, to reduce scan time, although this benefit is offset by reduction in signal-to-noise ratio; single velocity-encoding (VENC) set to 10% above the expected maximum velocity, which decreases scan time, but also negatively affects the velocity-to-noise ratio; and the application of phase-unwrapping algorithms as well as eddy current and Maxwell correction algorithms to improve accuracy.(16)

When compared to standard imaging modalities, such as TTE and PCMR, 4DF-CMR offers a number of advantages. It enables direct jet visualisation and quantification of regurgitant lesions, especially when complicated by eccentric or multiple jets.(22-24) This is possible as it can be visualised in a 3-dimensional (3D) dataset. When performed as a whole heart acquisition, it allows the evaluation of all four cardiac valves simultaneously within a single acquisition.(25) Simultaneous quantification of flow across all 4 valves in 4DF-CMR provides a means of internal validation of flow measurements.(16) Studies which evaluated all four valves, showed strong agreement between net flow volumes across all valves(25), with small inter-valvular variation(26).

Consistency across modalities is significantly improved when retrospective valve tracking (RVT) is used.(27) Furthermore, as all the measurements are obtained from the same acquisition, the impact of variability related to changes in heart rate, on consistency of measurements will be reduced.(28) Although blurring can occur as a result of irregular heart rate(29), a recent study showed that measurements of flow volumes remain accurate and feasible even in the presence of atrial fibrillation.(30) Moreover, peak velocity measurements in stenotic lesions may be more accurate and precise than with PCMR.(31) Several novel markers, such as wall shear stress can also be measured, which may be helpful in the assessment of patients with bicuspid aortic valve disease amongst other pathologies.(32-35) Finally, the acquisition itself requires only very simple planning.(29)

There are, however, a number of challenges encountered in 4DF-CMR. The main drawbacks of this technique include limited temporal and spatial resolution, long scan time(16) and the requirement for complex post-processing, which requires specialised knowledge and is time-consuming. Also, 4DF-CMR imaging requires supplementary cine images, which serve as an anatomical framework for the phase images. This can potentially lead to misalignment between the anatomical reference and the phase images due to heart rate variability and patient movement during the scan. Although misalignment can often be corrected during post-processing, it adds an extra step to the analysis.(28)

As with PCMR, an appropriate VENC needs to be chosen and should be set to a value that is marginally higher (about 10%) than the expected peak

velocity in the region of interest. Inappropriately low VENC setting can lead to aliasing, whereas the higher the VENC, the lower the velocity-to-noise ratio. It is therefore advisable to apply a phase-unwrapping algorithm, especially in cases where it might be difficult to estimate the maximum velocity.(16) Mixed valve disease can pose a further challenge to VENC setting, as a value appropriate for low velocities will not be optimal for a high velocity setting. Although this can be overcome by two separate acquisitions with different VENC settings, it is very time consuming.(36) Hence, clinically applicable dual- and multi-VENC sequences are emerging, which will be helpful when stenotic and regurgitant lesions co-exist.(16, 36, 37)

Although peak velocity assessment in stenotic lesions may be complicated by signal dephasing secondary to turbulent flow and could potentially lead to imprecise measurements, the visualisation and identification of the highest velocity area may also allow more accurate assessment of velocity.(38)

With regard to regurgitant lesions, visualisation of areas of turbulence and signal dephasing can help with accurate quantification, as these areas can be avoided.(9) Regurgitant lesions are also frequently complicated by multiple and/or eccentric jets, especially in the case of mitral valve.(39) Although direct jet quantification can be performed in these cases, it may be challenging(40) and time-consuming(41). The indirect method can be advantageous in these cases and has been shown to have a better intra- and inter-technique reliability.(42)

Furthermore, as with PCMR, phase offset errors may occur and must be corrected. Artefacts occurring due to Maxwell terms and non-linearity of the gradient field tend to be optimised easily, however, correction for eddy currents has to be performed manually and incorporated into data analysis.(43) The advantages and disadvantages of the various imaging modalities used in VHD assessment are shown in **Table 1-1.**

Table 1- 1 Advantages and disadvantages of different imaging modalities in assessment of valvular heart disease

Modality	Advantages	Disadvantages
Transthoracic echocardiography	➢ Widely available(6) ➢ Inexpensive(5) ➢ Safe(4)	➢ Limited accuracy in patients with large body habitus and chronic obstructive pulmonary disease(7) ➢ Limited accuracy in the presence of eccentric/multiple regurgitant jets(9) ➢ Suboptimal assessment of right heart(8)
Transoesophageal echocardiography	➢ Not limited by body habitus(44) ➢ Superior image quality when TTE is suboptimal(1) ➢ Visualisation of structures not assessed by TTE e.g. left atrial appendage(1)	➢ Risk of bleeding and oesophageal perforation(44) ➢ Requires presence of trained medical personnel(44) ➢ Potential complications of sedation(44) ➢ Reduced utility during pandemic due to high aerosol production(45)
Standard CMR (LV/RV cine stack, PCMR and LGE)	➢ Reference-standard left and right ventricular size and function assessment(14, 15) ➢ Accurate indirect quantification of atrio-ventricular valve regurgitation, even in the presence of eccentric and multiple jets(39) ➢ Tissue phenotyping/quantification of fibrosis(46)	➢ Inaccurate direct quantification of atrio-ventricular valvular regurgitation(13) ➢ Potential for error in stroke volume calculation(6) ➢ Limited by claustrophobia/arrhythmia (6, 47) ➢

4DF-CMR	➢ Regurgitant jet visualisation(22) ➢ Direct regurgitant jet quantification(9) ➢ No geometric assumptions(22) ➢ Simultaneous analysis of flow across all four valves(25) ➢ Accurate peak velocity assessment vs. PCMR(31) ➢ May be advantageous in combined valve lesions(22) ➢ Measurement of fluid biomechanics(29) ➢ Simple acquisition(29) ➢ Free-breathing(23) ➢ Plane reformatting is possible(25)	➢ Time-consuming post-processing(29) ➢ Limited temporal and spatial resolution(29) ➢ Limited software availability(16)

Abbreviations: 4DF-CMR=Four-dimensional flow cardiovascular magnetic resonance; AR=aortic regurgitation; AS=aortic stenosis; LV=left ventricle; PCMR=phase contrast magnetic resonance; RV=right ventricle; TTE=transthoracic echocardiography.

1.1.2 Mitral regurgitation and the rationale and clinical applications of 4DF-CMR in mitral regurgitation

Mitral regurgitation and aortic stenosis are the most common valvular pathologies in the developed world. As the population is ageing significantly, the prevalence of VHD is expected to increase.(48) Mitral regurgitation accounts for almost 25% of VHD cases in contemporary practice and is the second most common pathology in Europe.(49) Furthermore, untreated severe mitral regurgitation is associated with a high burden of morbidity and mortality.(50) The prevalance of MR can be as high as 10%.(51) Establishing aetiology of MR is crucial, as it determines the management. MR can be broadly divided into primary, also considered degenerative and secondary, functional MR.(3) In primary MR, the regurgitaiton is caused by an issue with the valve itself such as the leaflets, papillary muscles or

chordae tendinae, while in secondary MR it's related to the atria or ventricles. The most common aetiology of primary MR is mitral valve prolapse, which can occur as a result of myxomatous degeneration in younger population or fibroelastic deficiency in the older subset of patients. Less commonly, it can occur as a result of infective endocarditis, rheumatic heart disease or secondary to radiation.(3) Secondary MR most commonly occurs as a result of distortion of the left ventricular shape, size or function or atrial dilatation.(52) This can be a result of a cardiomyopathy, wall motion abnormality due to myocardial infarction or annular dilatation due to chronic atrial fibrillation.(52) While the management of secondary MR is mostly based on medical therapies, severe primary MR is managed surgically.

Current guidelines recommend surgery in symptomatic patients with severe chronic primary mitral regurgitation and those who are asymptomatic, but have evidence of left ventricular (LV) or left atrial (LA) remodelling, such as impaired left ventricular ejection fraction (LVEF) ≤60%, left ventricular end-systolic diameter ≥45mm, new-onset atrial fibrillation or elevated pulmonary pressures >50mmHg. In secondary mitral regurgitation, surgery is recommended in those with LVEF >30% undergoing coronary artery bypass grafting, those with LVEF <30%, but with viable myocardium and an option for revascularisation, and those who are considered at low surgical risk and failed a trial of optimal medical therapy.(1) These guidelines highlight the importance of accurate assessment of MR severity and LV cavity size and function, to guide surgical therapy decisions.

Quantification of mitral regurgitation, and therefore the indication for surgery or percutaneous intervention relies on transthoracic echocardiography

measurements in the majority of patients.(1, 3) In selected cases, however, further investigation, including the use of CMR may be indicated.(3, 40, 53, 54) CMR studies showed that PCMR reclassified a proportion of patients with MR into a different severity category, which in turn showed better association with prognosis. Uretsky et al in 2015 demonstrated discordance between MR quantification by PCMR and TTE and showed that CMR had a superior correlation with post-operative LV remodelling.(55) The prognostic advantage of CMR was confirmed in several other studies.(56-58) However, studies have reported different thresholds for classifying ‘severe’ mitral regurgitation. A study by Myerson et al, showed that a regurgitant volume (MR-Rvol) of more than 55ml and regurgitant fraction (MR-RF) of more than 40% was associated with adverse clinical outcomes (56), whereas a study by Aplin et al proposed lower threshold values.(59)

The above studies utilised indirect techniques for quantification of regurgitant volume and fraction. This was performed by subtracting aortic forward flow volume (obtained from through-plane velocity mapping) from left ventricular stroke volume (SV) derived from cine images. This decreased errors that could occur as a result of an eccentric jet, multiple jets or flow turbulence leading to signal void.(6) Although this standard PCMR assessment of mitral regurgitation is robust, it requires 2 types of acquisition and its accuracy may be limited by errors introduced in the process of stroke volume calculation.(9) Furthermore, different centres may use different methods of LV segmentation including or excluding left venricular outflow tract (LVOT)(60) and/or papillary muscles(61), which can lead to discrepancy in MR quantification. In the absence of tricuspid regurgitation (TR), it is also possible to quantify MR by subtracting right ventricular stroke volume (SV)

from LV stroke volume (6), although this is less commonly used. Direct assessment of the regurgitant flow by PCMR is not typically performed in clinical practice as it is inaccurate due to through-plane motion of the valve plane during systole, which can lead to significant quantitation errors.(61) This is further challenged by the mitral valve's complex anatomy.(22) Similarly to TTE, in the presence of eccentric jets, quantitation of MR by the direct approach may be imprecise due to signal void.(9)

4DF CMR overcomes a lot of these limitations and offers several advantages in the assessment of mitral regurgitation.(9, 62) A summary of the main studies that evaluated 4DF-CMR in the setting of mitral regurgitation is presented in **Table 1-2.**

Table 1- 2 4D Flow CMR studies in mitral regurgitation.

Valve pathology	Study	Nr of patients (n)	Population assessed	Reproducibility assessment	4DF vs. TTE	4DF vs. PCMR	Main findings
Mitral regurgitation	➢ 2008 Westenberg et al(63)	Controls n=10 Patients n=20	Ischaemic cardiomyopathy with MR and/or TR	+	-	+	➢ PCMR overestimated transmitral flow in healthy volunteers ➢ 4DF-CMR showed strong agreement between MV and TV flow in patients with MR and/or TR
	➢ 2009 Roes et al(25)	Controls n=22 Patients n=29	Ischaemic cardiomyopathy with valvular regurgitation	+	-	-	➢ Agreement amongst net flow volume for all valves was excellent ➢ Good intra- and inter-observer reliability for quantification of MR-RF
	➢ 2009 Marsan et al(64)	Patients n=64	Functional MR	-	+ (3D TTE)	-	➢ 2D TTE significantly underestimated MR
	➢ 2011 Brandts et al(65)	Patients n=47	Ischaemic heart failure	-	+	+	➢ Higher MR regurgitant fraction vs. PCMR ➢ Strong correlation between 4DF-CMR and TTE for LV diastolic assessment

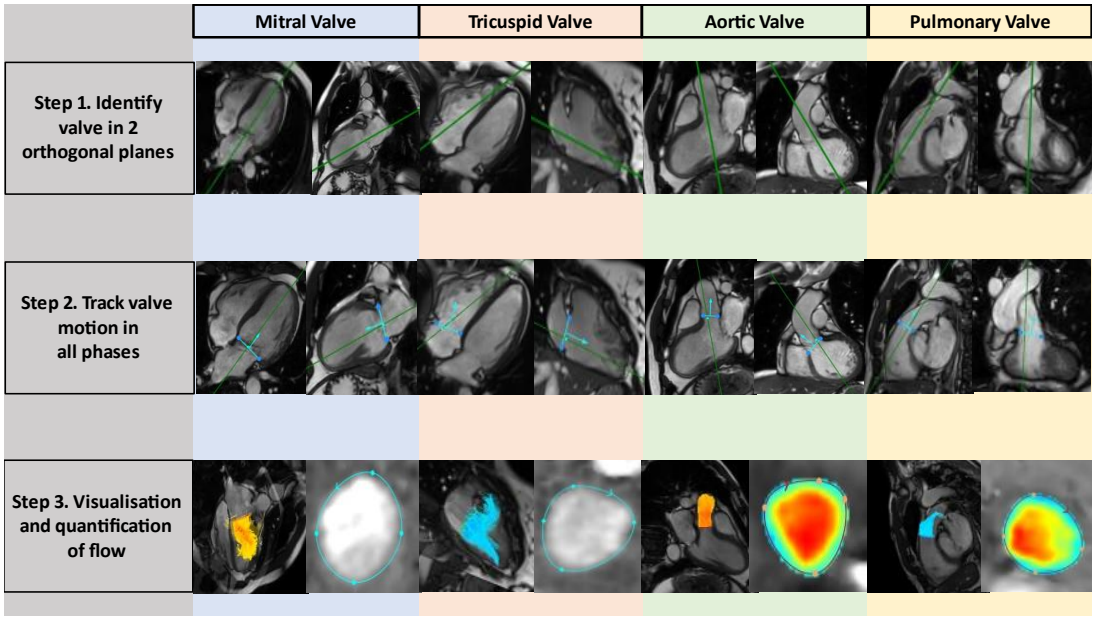
	➢ 2018 Gorodisky et al(66)	Patients n=27	Isolated MR of various severity	+	+	+	➢ CMR 4D-PISA was feasible ➢ CMR 4D-PISA was smaller than TTE-PISA
	➢ 2018 Feneis et al(9)	Patients n=21	Isolated MR n=10 MR+TR n=5 Isolated TR=6	+	-	+	➢ Good correlation between PCMR and 4DF-CMR quantification of regurgitation by direct and indirect methods
	➢ 2019 Kamphuis et al(67)	Controls=46 Patients n=114	Acquired and congenital pathologies	+	-	-	➢ Automated valve tracking is performed more rapidly than manual valve tracking ➢ Strong intra- and inter-observer correlation for regurgitant fraction quantification by automated valve tracking
	➢ 2020 Blanken et al(68)	Patients n=30	Various degrees of MR severity	+	-	+	➢ Valve tracking underestimated MR severity in cases of severe MR ➢ SFT RV correlated better with indirect quantification of RV by PCMR than RVT
	➢ 2021 Fidock et al(62)	Patients n=35	Primary MR n= 12 Secondary MR n=10	+	-	+	➢ Highest reproducibility was found for MV inflow-AV outflow method of MR quantification ➢ Good correlation between all methods in secondary MR and MVR

			MVR n=13				
	➢ 2021 Spampinato et al(42)	Controls=6 Patients=54	Mitral valve prolapse	+	+	+	➢ Indirect 4DF-CMR assessment of MR in MVP showed better intra- and inter-technique concordance than direct assessment
	➢ 2021 Juffermans et al(69)	Patients n=64 Controls n=76	Various pathologies	+	-	-	➢ Strong-to-excellent interobserver reliability for forward flow volume and net forward volume for all valves ➢ Moderate-to-excellent reliability for assessment of RF for all valves

CMR=cardiovascular magnetic resonance; MR=mitral regurgitation; MV=mitral valve; MVR=mitral valve replacement; PCMR=phase contrast magnetic resonance; PISA=proximal isovelocity surface area; RF=regurgitant fraction; MR-Rvol=regurgitant volume; RV=right ventricle; RVT=retrospective valve tracking; SFT=semi-automated flow tracking; TR=tricuspid regurgitation; TTE=transthoracic echocardiography; TV=tricuspid valve.

4DF-CMR data are mostly analysed via retrospective valve tracking (RVT). RVT can be performed manually or by an automated process. In the case of the mitral valve, manual RVT is performed by first reformatting the MV plane using the 4-chamber view and vertical long axis of the left ventricle. Manual placement of a line across the annulus in all the phases in the 4-chamber view marks the valve plane. This is cross-checked with the 2-chamber view to ensure correct positioning. This is subsequently performed manually in each phase. Once the valve is correctly tracked, a phase-contrast, valvular reformatted plane is created.(63) A study by Roes et al showed good intra- and inter-observer reproducibility for this technique.(25) Automated valve tracking (**Figure 1-1**) can be performed much more rapidly, and also with excellent intra- and inter-observer reproducibility.(67) Regurgitant flow can additionally be analysed by reformatting a plane, which is located above the annulus and is perpendicular to the regurgitant jet.(69, 70) Although most extensively studied in the setting of atrio-ventricular valves, retrospective valve tracking can also be applied to evaluation of semilunar valves. Recent studies showed, that aortic and pulmonary valve net forward flow and regurgitant flow can be directly quantified by RVT.(26, 67) Moreover, evaluation of valvular blood flow by automated RVT was shown to be reproducible and accurate for all valves, irrespective of scanner type and protocol.(69)

Figure 1- 1 4D Flow CMR visualisation and quantification of valvular flow by retrospective valve tracking.



Step 1. Identification of valve plane from cines acquired in 2 orthogonal planes. Step 2. Valve plane is tracked in all phases in the first view and cross-check with the second view. Arrow allows confirmation of flow in the correct direction. Step 3. Visualisation of flow enables accurate quantification of flow in phase-contrast images.

Different studies have explored different methods of MR volume quantification by 4DF. The main techniques include a) the indirect method (mitral regurgitant volume = 4DF-CMR mitral inflow volume – 4DF-CMR aortic outflow volume [MR_{MVAV}], b) the direct method, which quantified MR directly from 4DF phase contrast images and c) the 4D-CMR proximal isovelocity surface area (PISA) method. These techniques are described below:

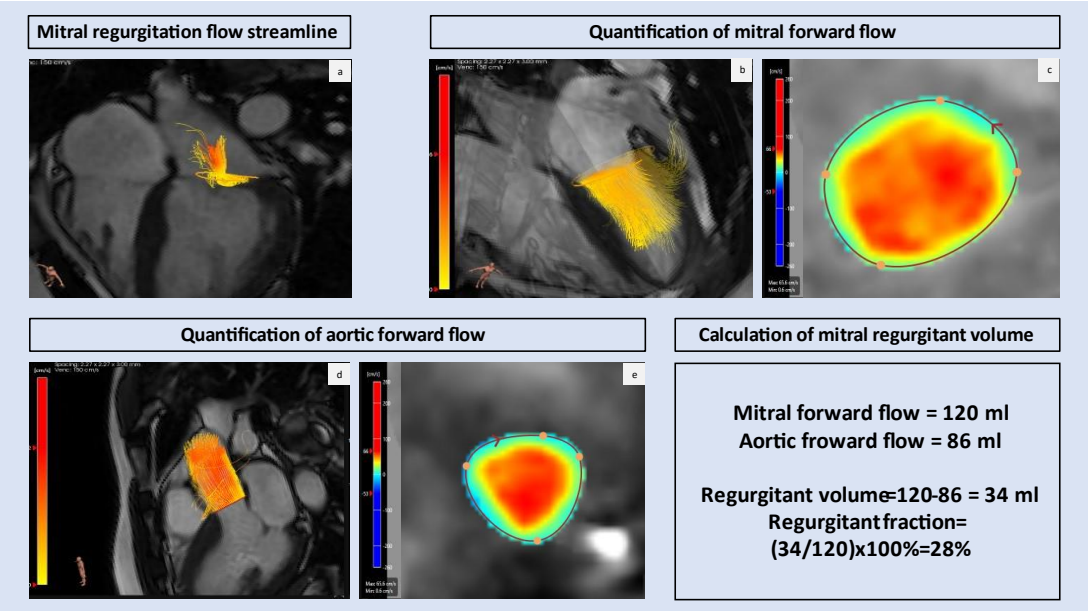
1) 4DF-CMR Indirect method (MR_{MVAV})

A recent study by Fidock et al, showed that MR volume assessed by the 4DF derived aortic outflow-mitral inflow calculation, correlated well with standard PCMR in primary MR, secondary MR and even in patients with

mitral valve replacement (MVR); and had the highest level of concordance with the standard PCMR measurements.(62) Another study of 54 patients with mitral regurgitation secondary to mitral valve prolapse (MVP), compared MR-Rvol and MR-RF by 4DF direct jet quantification and indirectly by 4DF derived difference in aortic stroke volume and mitral inflow. The direct jet interrogation technique was shown to have a lower inter- and intra-technique consistency than the 4DF-CMR indirect method. The indirect method agreed well with PCMR, whereas the direct technique yielded much lower regurgitant volumes. This was felt to be secondary to the physiology of MR jets, which tend to be multiple and eccentric in nature.(42)

Although direct quantification at jet level can be reliable and accurate, even in the presence of multiple and eccentric regurgitant jets(41), the indirect method offers an advantage, especially in cases of very complex regurgitant jets, where the direct jet method can be challenging to perform and labour intensive.(40, 62) An example of 4D Flow CMR indirect assessment of moderate mitral regurgitation is shown in **Figure 1-2.**

Figure 1- 2 4DF-CMR assessment of mitral regurgitation



Panel (a) shows four-dimensional mitral regurgitation flow streamline. Panel (b) demonstrates mitral forward flow visualised by 4DF-CMR and (c) quantification of mitral forward flow by phase-contrast image obtained from 4DF-CMR. Panel (d) shows aortic forward flow and (e) quantification of aortic forward flow by phase-contrast image obtained by 4DF-CMR.

2) Direct MR quantification

An early study by Roes et al showed that net flow through all valves can be assessed accurately with RVT and demonstrated good intra- and inter-observer consistency for regurgitant fraction in patients with MR.(25) A more recent study by Kamphuis et al compared net forward flow and regurgitant fraction by automated RVT versus manual valve tracking, and demonstrated that automated RVT can be performed much more rapidly than manual valve tracking, but also with high intra- and inter-observer reproducibility for regurgitant fraction.(67)

A small study of patients with ischaemic heart disease assessing LV diastolic parameters, found significantly lower transmitral flow rates and higher MV regurgitant fraction when compared to PCMR.(65) Similarly, a study of healthy volunteers and patients with mitral regurgitation showed that in volunteers MV flow was overestimated by 15% when assessed by PCMR.(63) However, when compared to TTE, the results were somewhat variable. Brandst et all found an excellent correlation between 4DF-CMR and TTE versus PCMR and TTE(65), whereas a study by Marsan et al found that 2-dimensional (2D) TTE significantly underestimated MV regurgitant volume in patients with functional MR as compared to 4DF-CMR.(64) All studies mentioned so far mainly used RVT at the valve level to quantify MR.

Feneis et al utilised direct jet analysis as well as the indirect method in the assessment of 21 patients with MR and/or TR and compared the results to conventional CMR. Direct jet assessment involved examination of the regurgitant flow at various anatomical locations, beginning at the valve plane and then with at least 5mm intervals. Areas of signal dephasing and aliasing velocity were avoided. The authors showed, that there was a good correlation between the measurements for those 2 modalities, for both, the direct and the indirect method. The intraobserver and interobserver reproducibility also proved very good to excellent for the direct jet approach.(9)

Direct jet interrogation was also used in a recent study by Fidock et al of 35 patients with primary MR, secondary MR and MVR. Fidock et all found that in cases of primary MR, direct jet interrogation overestimated MR volumes;

this was not the case for secondary MR or MVR patients. The authors proposed that the inconsistency in delineating the analysis plane was most likely responsible for this finding. The concordance of results in secondary MR was most likely related to the central MR jet and the particular cohort of patients in this study, as most patients with secondary MR had only a mild degree of regurgitation.(62)

A recent study by Blanken et al quantified MR by semi-automated flow tracking (SFT) and compared it to semi-automated valve tracking. In this retrospective study of 30 patients, the authors showed that flow tracking allowed superior assessment of MV regurgitation, especially in cases of severe MR. This study showed that MR-Rvol assessed by flow tracking was higher than the volume quantified by valve tracking and it correlated better with the regurgitant volume assessed by the standard method (LV stroke volume - Aortic outflow). MR volume was underestimated by the valve tracking technique in cases of severe MR. The interobserver reproducibility was superior for semi-automated flow tracking versus semi-automated valve tracking. The authors proposed that the superiority of flow tracking may be related to the enhanced precision of quantification of flow by relocating the analysis plane above the annulus and thus avoiding areas of turbulence and dephasing; and improved differentiation of the mitral regurgitant jet and aortic forward flow. The authors noted, however, that there were several limitations, which may have been responsible for the findings, including different aetiologies of mitral regurgitation in the different valve severity groups.(68)

3) PISA method

Although this is not an actual 4D Flow method per se, Gorodisky et all showed that CMR 4D-PISA is feasible as a surrogate marker of mitral regurgitant volume quantification. In this method, 3D flow vectors are obtained from each 3mm slice between the mitral valve annulus and the LV apex. Although the analysis is performed by automated software, the appropriate slices and time frames need to be chosen manually. CMR 4D-PISA excludes geometric assumptions that are invariably made by echocardiography with this method. When compared to TTE-PISA, the CMR-PISA was smaller. TTE-PISA frequently overestimates flow, as it is obtained at a single time-point and does not take into account variation of flow during systole. The shape of CMR-PISA was also noted to be a hemi-ellipsoid in contrast to the hemisphere on which the TTE-PISA assumptions are based. The authors suggested, that flow magnitude could be measured accurately, as 3D velocity encoding allowed for the true flow to be measured in each voxel, diminishing the errors caused by the angle between the flow direction and the imaging plane. However, one disadvantage of CMR-PISA method is the possibility of inaccurate localisation of the vena contracta, which can occur in some cases.(66) Of note, the accuracy of flow assessment may be influenced by the sequence used. A recent study showed, that accelerated echo-planar imaging sequence may lead to errors in flow and velocity measurements in certain cases.(71)

Finally, novel markers such kinetic energy mapping by 4D Flow CMR can also be utilised to aid the assessment of mitral regurgitation.(21) One study

showed that peak KE levels in the late diastolic period did not decline after mitral valve surgery, suggesting persistence of pathological blood flow after an intervention.(72)

As 4D Flow CMR offers a lot of advantages in quantification of MR, it may help to correlate long-term outcomes of patients with significant MR according to different thresholds of severity, and clarify what regurgitant volume and fraction are associated with adverse LV remodelling and may benefit from earlier surgical treatment.(9) While there are advantages and disadvantages associated with all the aforementioned techniques, the indirect method (MR_{MVAV}) has been shown to be most accurate and reproducible.

1.1.3 Limitations

Limited spatial and temporal resolution are significant drawbacks of 4D Flow CMR.(16) These can lead to underestimation of high-velocity regurgitant jets.(9)Long scan times may also limit the utility of this technique in a number of settings such as claustrophobic or unwell patients who may not tolerate such a lengthy scan.(29, 73) Newer acceleration techniques, however, enable faster acquisition without a compromise in terms of spatial or temporal resolution. Labour-intensive post-processing further limits the clinical applicability of 4DF.(29) Similar to PCMR, phase offset errors can cause substantial artefacts and need to be corrected. Although effects of eddy currents cannot be entirely removed, they can be minimised.(16)

1.1.4 Current status and future perspective

In routine clinical practice, an experienced 4DF user can complete quantification of aortic and pulmonary flow in about 5 minutes. Careful segmentation of mitral valve flow adds 5-10 minutes. If direct jet approach is used, it adds a few minutes to the post-processing time.

Despite all the developments of 4DF-CMR in the recent years, it has not become a routine component of CMR protocols. Expensive analysis software, time consuming post-processing and expert analysis required all hinder adoption of 4D Flow in everyday CMR practice. Development of an approachable, user-friendly software could encourage more imaging specialists to train in this novel technique, increasing its clinical utility.

1.1.5 Conclusions

Assessment of valvular heart disease by 4D Flow CMR is precise and reproducible. Although still a relatively novel technique and not routinely employed in contemporary clinical practice, it has the potential to become the new reference-standard method for the evaluation of valvular lesions. It overcomes a lot of the constraints of other imaging modalities, including TTE, TOE and PCMR. With new acceleration techniques and developments in automated post-processing methods, scan times and post-processing times are likely to be substantially shortened in the future, making this technique much more clinically applicable.

1.2 Exercise testing in asymptomatic mitral regurgitation

1.2.1 Timing of surgery in primary mitral regurgitation

In primary mitral regurgitation, surgery is recommended in patients with symptoms, and in asymptomatic patients who exhibit features of adverse LV remodelling, such as increased LV end-systolic diameter or impaired LVEF <60%.(1, 3) Mitral valve repair is also recommended in those with new onset atrial fibrillation or systolic pulmonary hypertension, if the likelihood of repair is high and the risk of mortality is less than 1%.(1) As in the asymptomatic patients the surgery is carried out solely for prognostic reasons, it is paramount that the severity of MR and its effect on the LA and the LV are assessed accurately. Furthermore, appropriate timing of surgical intervention is also crucial because irreversible LV remodelling may ensue before obvious changes in the LVEF or LV size, and thus before the surgery. As early, successful repair carried out at the appropriate time has excellent long-term prognosis(74), standard TTE assessment may not be sufficient in this group of patients to guide surgical therapy decisions.

1.2.2 Clinical utility of exercise testing in primary MR

Exercise testing, such as by cardiopulmonary exercise testing (CPEX) or treadmill testing can be utilised to evaluate if the asymptomatic patients with primary MR are truly asymptomatic. An exercise test can be useful to elicit occult symptoms(75), as studies have shown that up to 25% of apparently asymptomatic patients have reduced functional capacity(76). While the exercise tests are useful to evaluate functional capacity and assess symptoms, exercise imaging can add further diagnostic and prognostic information.(3)

1.2.3 Exercise echocardiography

Although standard resting transthoracic echocardiography (TTE) is sufficient in a large proportion of patients with MR, exercise transthoracic echocardiography (EX-TTE) can be advantageous in the asymptomatic patients, not only to assess symptomatology, but also to quantify changes in MR during exercise, assess for the development of elevated pulmonary pressures and unmask subclinical LV dysfunction.(1) Furthermore, lack of contractile reserve during exercise, defined as failure to augment LVEF by at least 4% during exercise has been shown to be associated with poor prognosis(4) and lower LVEF after surgery(6). Right ventricular dysfunction on exercise has also been associated with adverse prognosis and is an independent predictor of time-to surgery.(7) This is independent of resting LV strain, exercise pulmonary pressures and resting RV strain.(8) Exercise-TTE can therefore identify high risk patients, who may benefit from early surgical referral. EX-TTE, however, is bound by the same limitations as resting TTE, such as limited reproducibility and poor acoustic windows. These issues become even more pronounced during exercise due to motion artefact.(9) Indeed, one study has shown that it was not possible to assess severity of MR by EX-TTE in half of the patients; and it was particularly difficult in those with mitral valve prolapse.(10)

1.2.4 Exercise cardiovascular magnetic resonance imaging

CMR imaging is not only the reference-standard for the assessment of the LV and RV size and function at rest(15, 60), but quantification of MR by CMR has been shown to have prognostic associations, while standard TTE assessment did not.(56, 57) Although exercise-cardiovascular magnetic

resonance (EX-CMR) is challenging, acquisition of images during continuous in-scanner exercise is now possible.(77) Exercise-CMR can therefore offer numerous advantages in the assessment of MR. While it is constrained by the availability and cost of the ergometer, it provides means of physical, rather than pharmacological stress, which is more physiologically accurate and it allows imaging during, rather than post exercise.(78) Exercise-CMR has been used in various cardiovascular conditions, but up to date its utility in valve disease has been limited. A small study of 5 patients with MR performed biventricular assessment during continuous in-scanner exercise and demonstrated its feasibility. This study, however, did not quantify aortic flow, which prohibited accurate MR quantification.(77) While a meta-analysis of EX-CMR studies in healthy volunteers, demonstrated the typical changes that occur during supine exercise, including increase in stroke volume, as a result of reduction in the LV end-systolic volume, but with no significant change in the LV end-diastolic volume(79), the biventricular and MR changes that occur during supine, continuous EX-CMR in primary MR are presently unknown. Other than the small study of 5 patients with MR, which demonstrated a significant increase in the LVEF during exercise, with no change in the left ventricular end-diastolic volume (LVEDV) and a non-significant reduction in LVESV(77), there are no EX-CMR studies in MR.

1.2.5 Effective forward LVEF

The presence of subtle, subclinical LV dysfunction may occur before any detectable changes in the LVEF or the LV size. Especially in the case of MR, which is characterised by reduced afterload, the LVEF is not a true reflection of myocardial function and contractility.(80) As patients with subclinical LV

dysfunction represent a high-risk subset, they may benefit from early surgery. It is therefore crucial that subtle LV impairment is identified in a timely manner. Effective forward LVEF, which is a product of the aortic forward flow and LVEDV, has been proposed as a more accurate measure of the true LV function in the presence of MR. Reduced effective forward LVEF pre-operatively has been shown to be the best predictor of post-operative LVEF impairment.(81) The concept of effective forward LVEF, however, has never been examined during exercise. In primary MR, decreased effective forward LVEF during exercise could potentially be a marker of early LV dysfunction and thus identify patients who could benefit from an early surgical therapy. As biventricular and aortic flow assessment is feasible and reproducible by EX-CMR in healthy volunteers(82), EX-CMR could be utilised to quantify the effective forward LVEF in patients with MR during exercise. This may possibly have prognostic associations, however, further studies are needed to examine its clinical significance.

1.2.6 Conclusion

Although EX-CMR is challenging and requires specialised, expensive equipment, it has the potential to become the exercise imaging modality of choice, particularly in the asymptomatic patients with primary MR, where it may identify high-risk patients, who would benefit from early surgery. Larger studies are, however needed to correlate the biventricular and MR changes during exercise in these patients with clinical outcomes.

1.3 Silent cerebral infarction (SCI) in mitral valve surgery

Mitral regurgitation is the second most common valvular pathology in the developed world.(83) When untreated, severe MR is associated with adverse outcomes.(50) Current European and International guidelines recommend surgery in symptomatic patients and those with evidence of LA and LV remodelling.(1, 3) Appropriate timing of surgery is crucial with a goal to prevent irreversible LV and LA fibrosis.

1.3.1 Stroke in mitral valve surgery

Stroke is a well-documented complication of mitral valve surgery. Although quite rare, it is associated with devastating consequences and excess of morbidity and mortality.(84) Peri-operative silent cerebral infarction (SCI) has been shown to be much more common in cardiac surgery, but with conflicting evidence as to its clinical significance and impact on neurocognitive function and quality of life.(85-88)

1.3.2 Silent cerebral infarction in cardiac surgery

Transcranial Doppler studies have shown that silent cerebral infarction is characterised by embolization of small and numerous platelet aggregates, air emboli and fat particles, which originate during surgery from aortic cannulation and cross-clamping of the aorta, amongst others.(89) Several studies utilised diffusion-weighted magnetic resonance imaging (DWI-MRI) and showed that these micro-emboli result in low-volume, numerous and multi-territorial microinfarcts, which present as acute high-intensity changes on DWI-MRI.(90) As they are not accompanied by focal neurological deficit,

they are termed ‘silent’, although their medium-term and long-term health consequences remain unknown.

Although several studies evaluated the incidence and clinical impact of silent cerebral infarction in cardiac surgery, these studies included primarily patients undergoing coronary artery bypass graft(88), aortic valve surgery(91, 92), combined surgery(87, 93) and transcatheter aortic valve implantation(94, 95). Up to date, there are no dedicated studies describing the incidence or characteristics of silent cerebral infarction in mitral valve surgery and particularly, in mitral valve repair.

While the available studies reported the incidence and consequences of SCI in different cardiac surgeries, the incidence of SCI was very variable, even in the same type of surgery.(88, 96) Furthermore, similar to the heterogeneity in the incidence, the impact on quality of life and neurocognitive function varied widely in these studies.(87, 97)

1.3.3 Conclusion

While some of the aforementioned studies did include patients undergoing mitral valve surgery, the number of patients was very small, and the results did not differentiate between those having MV surgery and those undergoing other operations. Thus, up to date, there are no informative data with regard to the incidence of SCI in MV surgery, its characteristics, potential differences between mitral valve repair and mitral valve replacement, and its clinical significance.

1.4 Summary and aims

In summary, although a lot of advancements have been made in the above areas, unanswered questions remain. Amongst others, these include the presence or absence of association of 4DF CMR MR-Rvol with post-operative remodelling, the feasibility and reproducibility of biventricular and aortic flow assessment by Ex-CMR in patients, rather than healthy volunteers, the possibility of 4DF CMR during continuous in-scanner exercise and the incidence and clinical implications of silent cerebral infarction in mitral valve surgery. These questions have led to the following hypotheses: 1) As 4DF CMR has been shown to agree well with PCMR in the assessment of MR-Rvol, there is an association between 4DF CMR-derived MR-Rvol and the post-operative LV remodelling, 2) as Ex-CMR assessment of biventricular volume and aortic flow is feasible in healthy volunteers, it should be possible in asymptomatic patients, 3) the incidence of silent cerebral infarction in mitral valve surgery is similar to the incidence of SCI in other on-pump cardiac surgeries. Therefore, the aims of this thesis are as follows: to establish whether 4-dimensional flow CMR MR-Rvol is associated with post-operative LV remodelling in primary MR, to evaluate feasibility and reproducibility of exercise-CMR in asymptomatic, primary MR, to attempt to develop a clinically applicable pulse sequence for acquisition of 4DF-CMR during continuous exercise and to assess the incidence and characteristics of silent cerebral infarction in mitral valve surgery for primary MR.

Chapter 2
Clinical utility of 4D flow cardiovascular magnetic resonance in primary mitral regurgitation: an observational, cohort study

2.1 Abstract

Introduction: While phase-contrast cardiovascular magnetic resonance (PCMR) imaging overcomes several limitations encountered by transthoracic echocardiography (TTE), the novel 4-dimensional flow cardiovascular magnetic resonance (4DF-CMR) offers additional advantages in primary MR. To our knowledge, the relationship between the pre-operative 4DF-CMR-derived MR regurgitant volume (MR-Rvol) and the post-operative left ventricular (LV) reverse remodelling has not yet been established. Therefore, we sought to assess the agreement between the MR-Rvol quantitated by 4DF-CMR with PCMR and TTE-derived MR-Rvol, and to ascertain if the 4DF-CMR-derived MR-Rvol correlates with the LV reverse remodelling in primary MR.

Methods: Prospective, single-centre, observational study of patients with at least moderate primary MR; patients were either awaiting mitral valve surgery (repair (MVr), replacement (MVR)) or were undergoing ‘watchful waiting’ (WW). All patients included in the study underwent TTE, PCMR, 4DF-CMR and 6-minute walk test (6MWT) at baseline, and a follow-up PCMR and 6MWT at 6-months. MR-Rvol was quantified by PCMR (LV stroke volume-aortic forward flow), 4DF-CMR (mitral forward flow-aortic stroke volume) and by TTE (proximal isovelocity surface area). The

agreement between methods was evaluated in all patients. In the surgical patients, the pre-operative MR-Rvol was correlated with the post-operative decrease in the LV end-diastolic volume index (LVEDVi).

Results: Forty-four patients were enrolled (MVr n=16, MVR n=13, WW n=15). While Bland-Altman plots demonstrated similar between all the modalities and the limits of agreement were relatively wide, they were narrower between 4DF-CMR and PCMR (bias 15; limits of agreement -36ml-65ml), than between 4DF-CMR and TTE (bias -8; limits of agreement -106-90ml) and PCMR and TTE (bias -23; limits of agreement -105ml-59ml). Linear regression analysis demonstrated a significant association between the pre-operative MR-Rvol volume and the post-operative decrease in the LVEDVi, when the MR-Rvol was quantified by PCMR (p=0.001) and 4DF-CMR (p=0.04), but not when assessed by TTE (p=0.73). Furthermore, 4DF-CMR demonstrated the best diagnostic performance for reduction in the post-operative LVEDVi with the largest area under the curve (4DF-CMR 0.83;p=0.04 vs. PCMR 0.78;p=0.03 and TTE 0.51;p=0.89).

Conclusions: This study demonstrates the potential clinical utility of 4DF-CMR in the assessment of primary MR, showing good agreement with PCMR and association with post-operative LV reverse remodelling.

2.2 Introduction

When untreated, severe mitral regurgitation (MR) is associated with excess morbidity and mortality.(50) Accurate and timely assessment of mitral regurgitation is therefore crucial in guiding surgical therapy decisions. This is

especially important in asymptomatic patients undergoing surgery for prognostic reasons.(52) Guidelines recommend transthoracic echocardiography (TTE) as the first-line modality for quantification of MR.(1, 3) Although TTE is sufficient in the majority of cases, it is limited by operator-dependence, body habitus and presence of multiple or eccentric regurgitant jets.(53)

Phase-contrast cardiovascular magnetic resonance (PCMR) imaging provides an advantage in these challenging cases and enables not only an accurate evaluation of MR severity, but also its impact on left ventricular (LV) size and function.(98) Prior studies showed a poor correlation between MR quantification by PCMR and TTE(55, 57), primarily in patients with eccentric, multiple or late-systolic jets, which are inherent in degenerative MR(57), and demonstrated a prognostic advantage of PCMR.(55) Four-dimensional flow cardiovascular magnetic resonance (4DF-CMR) is a novel technique that allows 3-dimensional and time-relative assessment of flow across all four valves within one, simple, free-breathing acquisition.(16) In contrast to PCMR, direct assessment of flow across the atrio-ventricular valves is accurate, as retrospective valve tracking accounts for the motion of the annulus during the cardiac cycle.(22) Studies which compared 4DF-CMR and PCMR, showed that the assessment of mitral regurgitant volume (MR-Rvol) by 4DF-CMR was feasible and reproducible(9, 70), with 4DF-CMR having better intra- and inter-observer reproducibility than PCMR(70). Moreover, it remained accurate even in the presence of atrial fibrillation.(99) Although 4DF-CMR is constrained by background phase-offset errors, limited temporal and spatial resolution, and laborious post-processing(16), it

has the potential to become the reference-standard in the assessment and quantitation of MR. To our knowledge, there are no studies, which have examined the relationship between the 4DF-CMR-derived pre-operative MR regurgitant volume with the post-operative LV reverse remodelling in primary MR. Therefore, we sought to determine the agreement between 4DF-CMR-derived MR-Rvol with PCMR- and TTE-derived MR-Rvol, and to ascertain if the 4DF-CMR-derived MR-Rvol is associated with the post-operative LV reverse remodelling in primary MR.

2.3 Methods

2.3.1 Study design and population

This was a prospective, single-centre, observational cohort study, which recruited patients with at least moderate primary mitral regurgitation, who were either awaiting mitral valve (MV) surgery, including mitral valve repair (MVr) and mitral valve replacement (MVR) and patients who were undergoing ‘watchful waiting’ (WW) and thus constituted the control group.

The grading of at least moderate mitral regurgitation was confirmed by the multi-disciplinary heart team based on transthoracic and/or transoesophageal echocardiography according to American Society of Echocardiography criteria.(100) Therapeutic decisions were made by the multi-disciplinary heart team in accordance with the European Society of Cardiology guidelines(1) and were independent from the study. Patients who were asymptomatic and did not have indications for surgery were managed medically and underwent WW.

Exclusion criteria included more than mild aortic valve disease and general contraindications to CMR. The study was approved by the National Research Ethics Service (15/YH/0503), had institutional approval and complied with the Declaration of Helsinki. All patients provided written informed consent.

2.3.2 Mitral valve surgery

MV surgery was performed according to the standard surgical practice, including midline sternotomy, cardiopulmonary bypass technique, systemic heparinisation and mild systemic hypothermia. The procedure was performed under intra-operative transoesophageal echocardiography guidance. MVr was performed using Gore-Tex chordae sutures and a Carpentier-Edwards annuloplasty ring, while MVR was performed using Edwards Perimount Magna bioprosthetic valve, St. Jude Epic™ Mitral stented tissue valve with Linx™ AC technology or St. Jude mechanical valves. Other interventions, such as tricuspid valve repair, coronary artery bypass grafting, and surgical left atrial ablation were performed if clinically indicated.

2.3.3 Study assessments

All patients included in the study underwent paired assessments. The baseline assessment was conducted at the time of recruitment in the WW group and prior to the surgery in the MV surgical groups; this consisted of PCMR, 4DF-CMR, TTE and a 6-minute walk test (6MWT). The follow-up assessment was undertaken at 6-months after the baseline visit in the WW

group and 6-months after the surgery in the MVr and MVR groups; this consisted of PCMR and a 6MWT.

PCMR

PCMR scan protocol (1.5T Philips Ingenia, Best, Netherlands) included:

a) Survey images
b) Free-breathing transverse Half-Fourier Acquisition Single-shot Turbo spin Echo imaging
c) Cine images acquired with breath-hold balanced steady-state free precession (bSSFP) sequence:
    a. 4-chamber view and vertical-long axis view
    b. 2 orthogonal left ventricular outflow tract views
    c. 2 orthogonal right ventricular outflow views
    d. Left ventricular short-axis stack. Sequence parameters: typical field-of-view 340mm, 10mm slice thickness with 0mm gap, repetition time 3msec, echo time 1.6ms, flip angle 60°, sensitivity encoding factor 2, in-plane acquired spatial resolution 1.88 x 1.88mm, 30 reconstructed phases and matrix 192x131.
    e. Transaxial right ventricular cine stack. Sequence parameters: typical field-of-view 360mm, 8mm slice thickness with 0mm gap, repetition time 2.8ms, echo time 1.41ms, flip angle 60°, sensitivity encoding factor 1.8, in-plane acquired spatial resolution 1.88 x 1.88mm, 20 reconstructed phases and matrix 192x143.
d) Through-plane aortic phase contrast images: planned at sino-tubular junction and orthogonal to the vessel.(40) In patients with atrial

fibrillation, 2 acquisitions were acquired. Velocity encoding was set to 150cm/s and increased as required. Sequence parameters: typical field-of-view 350x280mm, slice thickness 8mm, repetition time 5.1ms, echo time 3.2ms, flip angle 15°, temporal resolution 28ms, number of signal averages 1, sensitivity encoding factor 2, in-plane acquired spatial resolution 2.5×2.5mm, 30 reconstructed phases, phase percentage 100%, matrix 140x112, Cartesian sampling, turbo field echo factor 3 and acquisition duration 30.8ms.

e) Through-plane pulmonary phase contrast images: planned approximately 1cm above the pulmonary valve and orthogonal to the vessel. Sequence parameters as per through-plane aortic PCMR.

PCMR image analysis

Images were analysed blinded to clinical details using standard cvi42 software (Circle Cardiovascular Imaging, Calgary, AB, Canada). LV volumes were analysed by manual tracing of the endocardial border in end-diastole and end-systole on LV short-axis stack, with LV trabeculations being included in the blood pool, as described previously.(60) Left ventricular mass was estimated by manual tracing of the epicardial and endocardial border in end-diastole.(60) Right-ventricular volumes were analysed by manual tracing of the endocardial border in end-diastole and end-systole on the RV transaxial cine stack.(101) Aortic and pulmonary forward flow volumes were estimated using the semi-automated feature of the software, with subsequent manual correction. In patients with atrial fibrillation, 2 flow acquisitions were analysed and the final flow volume was taken as the average of the 2 measurements.

PCMR mitral regurgitant volume quantification

Mitral regurgitant volume was estimated indirectly(56), as follows: MR-Rvol=LV stroke volume - Aortic forward flow volume; where LV stroke volume=LV end-diastolic volume - LV end-systolic volume.

4DF-CMR

4DF-CMR was acquired with multishot echo-planar imaging pulse sequence (factor 5). Images were planned in a transverse orientation. Sequence parameters were as follows: retrospective gating, typical field-of-view 400mm, 39 slices, shortest repetition time, shortest echo time, flip angle 10°, 30 reconstructed phases, isotropic acquired voxel size 3x3x3mm, Cartesian acquisition, velocity encoding 150cm/s. The above multishot echo-planar imaging pulse sequence was previously validated by Garg and colleagues.(102)

4DF-CMR image analysis

All 4DF-CMR data were analysed blinded to clinical details by MG (fellow) and reviewed by MB (4DF expert). Images were analysed using standard Caas MR Solutions software (Pie Medical Imaging, Maastricht, The Netherlands). Aortic valve, pulmonary valve and mitral valve annulus were tracked using automated retrospective valve tracking in two orthogonal views.(67) Automated tracking was reviewed in each phase, and manually corrected as required. Flow was estimated for the aortic, pulmonary and mitral valve. Flow contours were adjusted manually in each phase. Pulmonary valve flow was estimated to provide means of internal validation of results.

4DF-CMR mitral regurgitant volume quantification

Mitral regurgitant volume was quantitated indirectly, where MR-Rvol=mitral forward flow volume (4DF-CMR-derived) - aortic stroke volume (4DF-CMR-derived). This method was chosen due to its previously demonstrated superior reproducibility and high level of precision.(70)

Transthoracic echocardiography

TTE was performed by a cardiac physiologist in a standard manner as per the British Society of Echocardiography guidelines.(103)

TTE mitral regurgitant volume quantification

This was based on the proximal isovelocity surface area (PISA) method(104), where MR-Rvol=effective regurgitant orifice area x velocity-time integral with effective regurgitant orifice area=($2\pi r^2$xNyquist limit)/peak velocity and where r=PISA radius.

Six-minute walk test

Functional exercise capacity was assessed using the 6-minute walk test (6MWT) distance (m) performed in accordance with the American Thoracic Society guidelines.(105)

Clinical Outcomes

Major Adverse Cardiovascular Events (MACE) were defined as the composite of all-cause death, myocardial infarction, stroke/transient ischaemic attack, hospitalisation for heart failure and acute hospitalisation for arrhythmia.

2.3.4 Statistical analysis

Continuous variables are presented as mean±SD or median with interquartile range as per normality of distribution. Normal distribution was

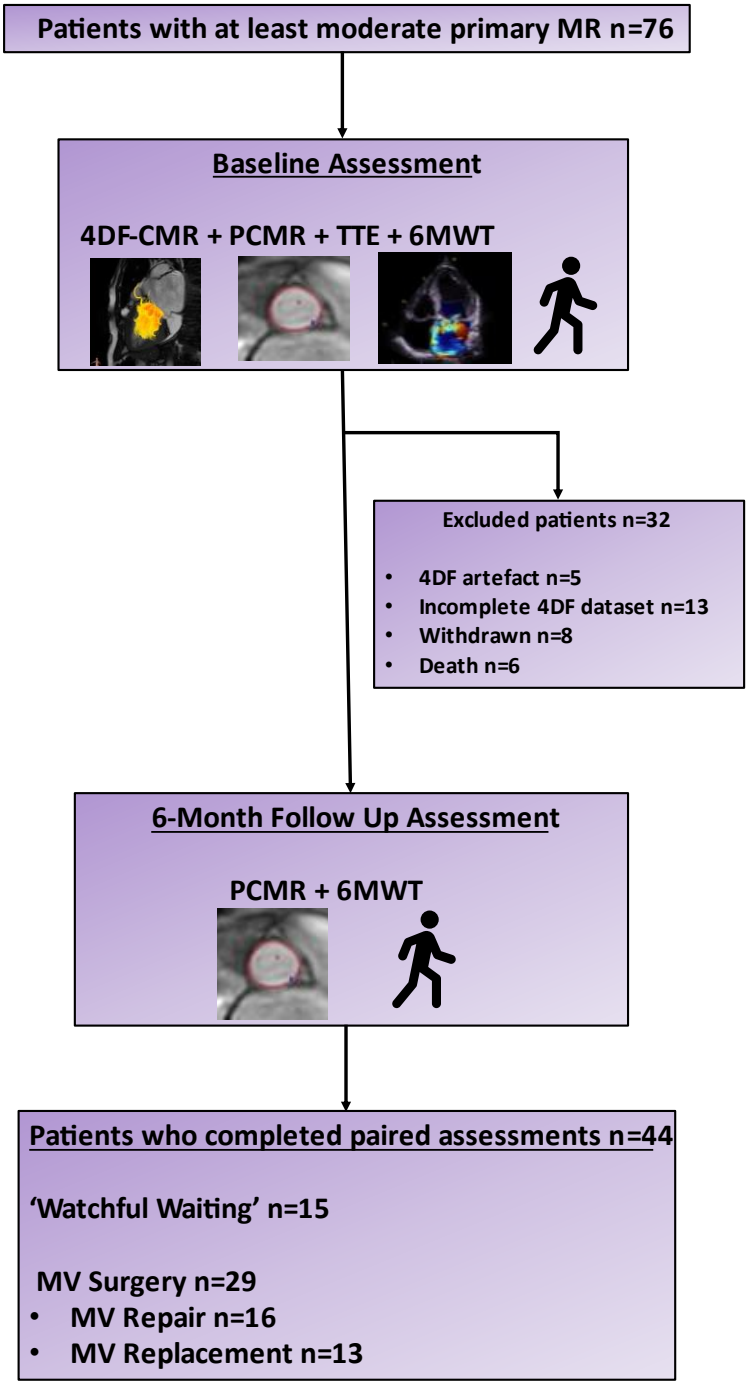
determined by Anderson-Darling test. Categorical data are presented as numbers and percentages. Continuous variables were compared by means of Student *t*-test (normal distribution) or Mann-Whitney test (non-normal distribution). Categorical variables were compared using Fisher's Exact test. The agreement between the MR-Rvol between the different modalities was compared with Bland-Altman plots. Linear regression analysis was performed to examine the association between the pre-operative MR-Rvol and the post-operative reduction in the LV end-diastolic volume index. Receiver operating characteristic curves were utilised to assess the diagnostic performance of each modality. Blinded intra-observer analysis was performed by MG. The reproducibility was assessed by intra-class correlation (ICC) with a two-way random model for absolute agreement and a 95% confidence interval (CI). All analyses were performed using Minitab (version 19) and statistical significance was defined as $P<0.05$.

2.4 Results

2.4.1 Demographic, clinical characteristics and surgical procedural data

Paired assessments were completed by 44 patients, of whom 15 were in the WW group and 29 in the MV surgery group **(Figure 2-1)**.

Figure 2- 1 Patient flow and study assessments.



4DF-CMR=4-dimensional flow cardiovascular magnetic resonance imaging; 6MWT=6-minute walk test; MR=mitral regurgitation; MV=mitral valve; PCMR=phase-contrast cardiovascular magnetic resonance imaging; TTE=transthoracic echocardiography.

'Watchful Waiting' vs. MV Surgery

The demographic and clinical characteristics were comparable between the WW and the MV surgery group **(Table 2-1)**. In both groups, the majority of patients were males in their late sixties. There were no significant differences in the body mass index score, EuroSCORE II or the prevalence of co-morbidities between the groups. As expected, patients in the WW were mostly asymptomatic with New York Heart Association class I dyspnoea (WW n=11(73.3%) vs. MV surgery n=10(34.5%); p=0.03). The most common aetiology of MR in both groups was posterior mitral valve prolapse (WW n=9(60%) vs. MV surgery n=19 (65.6%); p=0.75); bileaflet prolapse was the second most prevalent aetiology.

Table 2- 1 Baseline patient characteristics in patients undergoing 'watchful waiting' and MV surgery.

Variable	**Watchful Waiting n=15**	**MV Surgery n=29**	**p-value**
Age (years)	67(47-80)	69(64-72)	0.82
Male, n(%)	9(60)	21(72.4)	0.50
BMI (kg/m^2)	23.8±3.7	25.7±5.4	0.17
EuroSCORE II	0.99(0.50-2.74)	1.00(0.69-1.33)	0.61
NYHA Class I, n(%)	11(73.3)	10(34.5)	**0.03**
NYHA Class II, n(%)	3(20.0)	13(44.8)	0.19
NYHA Class III, n(%)	1(6.7)	6(20.7)	0.39
NYHA Class IV, n(%)	0(0)	0(0)	-
Hypertension, n(%)	2(13.3)	9(31.0)	0.28
Type 2 Diabetes Mellitus, n(%)	0(0.0)	2(6.9)	0.54
Atrial fibrillation, n(%)	3(20.0)	13(44.8)	0.19
Prior stroke/TIA, n(%)	2(13.3)	1(3.4)	0.26
Prior MI, n(%)	1(6.7)	0(0.0)	0.34
COPD, n(%)	1(6.7)	0(0.0)	0.34

Creatinine (µmol/L)	79±15	79±21	0.97
Haemoglobin (g/L)	135±12	141±9	0.07
MR Aetiology			
Posterior MVP, n(%)	9(60.0)	19(65.5)	0.75
Anterior MVP, n(%)	1(6.7)	2(6.9)	1
Bileaflet MVP, n(%)	5(33.3)	8(27.6)	0.74
Flail leaflet, n(%)	3(20.0)	10(34.5)	0.49

Data are presented as mean±SD, median(IQR1-IQR3) and n(%). BMI=body mass index; COPD=chronic obstructive pulmonary disease; EuroSCORE=European System for Cardiac Operative Risk Evaluation; MI=myocardial infarction; MR=mitral regurgitation; MVP=mitral valve prolapse; NYHA=New York Heart Association; TIA=transient ischaemic attack.

MV Repair vs. MV Replacement

There were no significant differences in the demographic or clinical characteristics between the MVr and the MVR group **(Table 2-2)**. A larger proportion of patients in the MVr group had posterior mitral valve prolapse (MVr n=13(81.2%) vs. MVR n=6(46.2%); p=0.06). The presence of a flail leaflet was also proportionally, but not significantly more prevalent in patients undergoing repair (MVr n=7(43.4%) and MVR n=3(23.1%); p=0.43). There were also no significant differences in the surgical procedural characteristics between these groups **(Table2-2)**. A small proportion of patients in both groups underwent a concomitant surgical procedure (coronary artery bypass grafting and/or tricuspid valve repair), whereas 1 patient in the MVR group also underwent

surgical atrial fibrillation ablation. More than half of the patients with MVR received a mechanical prosthesis (n=7(53.8%)).

Table 2- 2 Baseline patient and operative characteristics in patients undergoing MV repair and replacement.

Variable	**MV Repair n=16**	**MV Replacement n=13**	**p-value**
Age (years)	68(59-71)	69(63-74)	0.60
Male, n(%)	13(81.3)	8(61.5)	0.41
BMI (kg/m^2)	24.5(21.1-29.0)	25.6(21.8-27.9)	0.78
EuroSCORE II	0.94(0.68-1.37)	1.00(0.78-2.16)	0.79
NYHA Class I, n(%)	7(43.8)	3(23.1)	0.43
NYHA Class II, n(%)	8(50.0)	5(38.5)	0.71
NYHA Class III, n(%)	1(6.3)	5(38.5)	0.06
NYHA Class IV, n(%)	0(0)	0(0)	-
Hypertension, n(%)	7(43.4)	2(15.4)	0.13
Type 2 Diabetes Mellitus, n(%)	0(0.0)	2(15.4)	0.19
Atrial fibrillation, n(%)	6(37.5)	7(53.8)	0.47
Prior stroke/TIA, n(%)	1(6.3)	0(0.0)	1
Prior MI, n(%)	0(0)	0(0)	-

COPD, n(%)	0(0)	0(0)	-
Creatinine (µmol/L)	76±17	84±25	0.32
Haemoglobin (g/L)	140±9	143±10	0.45
MR Aetiology			
Posterior MVP, n(%)	13(81.3)	6(46.2)	0.06
Anterior MVP, n(%)	0(0.0)	2(15.4)	0.19
Bileaflet MVP, n(%)	3(18.6)	5(38.5)	0.41
Flail leaflet, n(%)	7(43.4)	3(23.1)	0.43
Operative data			
Concomitant CABG, n(%)	1(6.3)	2(15.4)	0.57
Concomitant TV repair, n(%)	3(18.8)	1(7.7)	0.61
Concomitant surgical AF ablation, n(%)	0(0.0)	1(7.7)	0.45
Concomitant aorta surgery, n(%)	0(0)	1(7.7)	0.45
Cumulative bypass time (min)	119(100-146)	110(99-127)	0.37
Cumulative cross clamp time (min)	87(69-108)	74(67-90)	0.17
Attempted repair, n(%)	-	1(7.7)	-

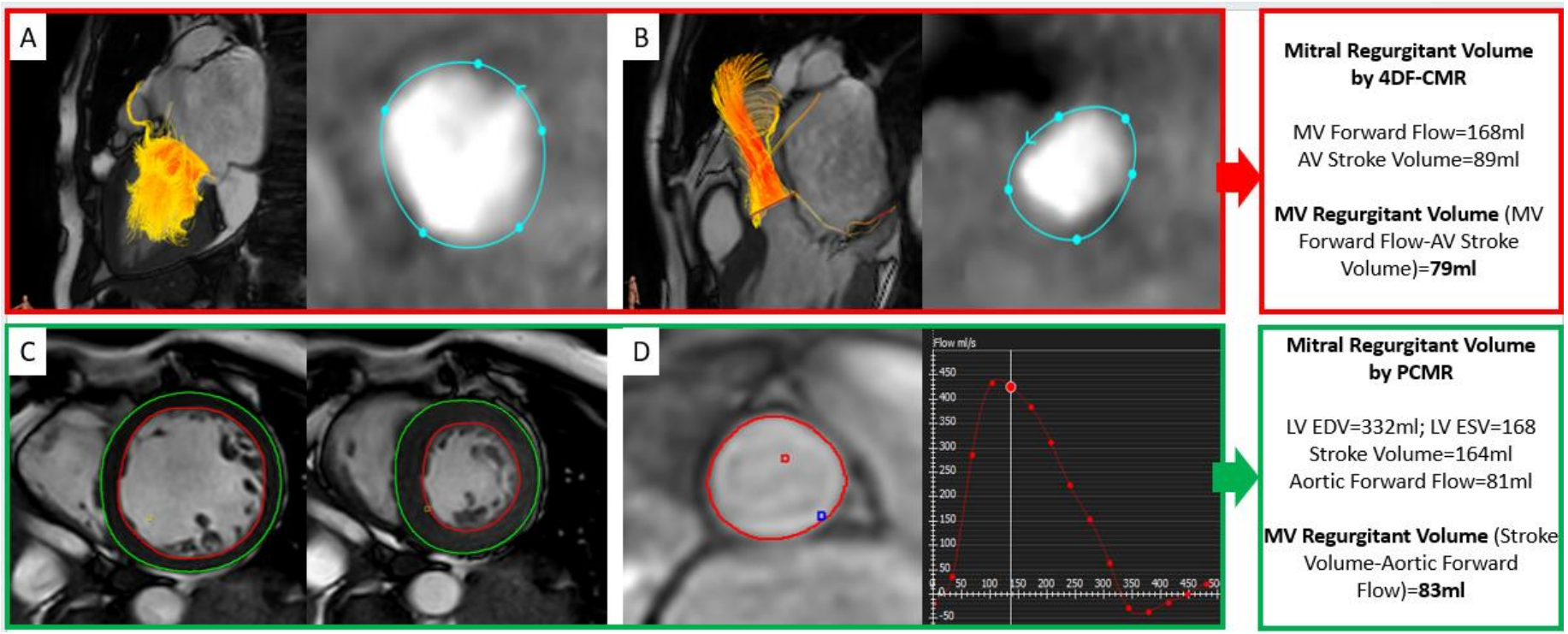
Mechanical valve, n(%)	-	7(53.8)	-

Data are presented as mean±SD, median(IQR1-IQR3) and n(%). AF=atrial fibrillation; BMI=body mass index; CABG=coronary artery bypass graft; COPD=chronic obstructive pulmonary disease; EuroSCORE=European System for Cardiac Operative Risk Evaluation; MI=myocardial infarction; MR=mitral regurgitation; MV=mitral valve; MVP=mitral valve prolapse; NYHA=New York Heart Association; TIA=transient ischaemic attack; TV= tricuspid valve.

2.4.2 Baseline imaging characteristics

All 44 patients included in the study underwent baseline PCMR, 4DF-CMR and TTE. Baseline imaging parameters in all groups are shown in **Table 2-3**. An example of quantification of MR volume by PCMR and 4DF-CMR is presented in **Figure 2-2**.

Figure 2- 2 An example of assessment of mitral regurgitation by 4DF-CMR and PCMR.



An example of assessment of mitral regurgitation by the different modalities. Top row presents assessment by 4DF-CMR. Panel (A) shows forward flow through the mitral valve and its quantification. Panel (B) shows aortic valve forward flow and its quantification. Middle row presents assessment by PCMR. Panel (C) shows quantification of left ventricular end-diastolic and end-systolic volume. Panel (D) shows quantification of aortic forward flow on phase-contrast image and the corresponding flow-time graph.

4DF-CMR=4-dimensional flow cardiovascular magnetic resonance imaging; AV=aortic valve; LV EDV=left ventricular end-diastolic volume; LV ESV=left-ventricular end-systolic volume; MV=mitral valve; PCMR=phase-contrast cardiovascular magnetic resonance imaging.

'Watchful Waiting' vs. MV Surgery

With regard to the PCMR characteristics, patients in the WW group had significantly smaller mean LV end-diastolic volumes (WW 208±42ml vs. MV surgery 247±72ml; p=0.03), but not when indexed to body-surface area (WW 114±20ml vs. MV surgery 130±34ml; p=0.05). Left ventricular mass and LV mass index were both significantly lower in the WW group (p=0.004 for both). There were no significant differences between the LV ejection fraction or stroke volume. The right ventricular ejection fraction was significantly higher in the WW group (WW 54±6% vs. MV surgery 47±5%; p=0.001). Mitral regurgitant volume was significantly lower in the WW group, than in the MV surgery group (WW 44±12ml vs. MV surgery 70±28ml; p<0.001), as was the indexed MR-Rvol and the mitral regurgitant fraction.

With regard to the 4DF-CMR parameters, the median aortic stroke volume was significantly higher in the WW group (WW 75ml (61-82) vs. 56ml (44-69); p=0.046). Similar to the PCMR findings, MR-Rvol and regurgitant fraction were significantly lower in the WW group (p=0.048 and p=0.045, respectively).

With regard to the TTE parameters, the LV end-systolic diameter was significantly smaller in the WW group (WW 34±6mm vs. MV surgery 39±7mm; p=0.02). The median mitral regurgitant volume was much smaller in the WW group than in the MV surgery group (67ml (47-85) vs. 80ml (68-112), respectively; p=0.04).

MV Repair vs. MV Replacement

When assessed by PCMR, there were no significant differences between the left ventricular, right ventricular or mitral regurgitant volume parameters between these groups.

Similar to PCMR results, when assessed by 4DF-CMR, there were no significant differences in the mitral forward flow volume or the aortic stroke volume. Mitral regurgitant volume, indexed volume and fraction were similar between the repair and the replacement group.

With regards to the TTE characteristics, there were also no significant differences between the 2 groups, although the mean MR-Rvol was numerically higher in the MVr group (MVr 103±44ml vs. MVR 78±30ml; p=0.08).

Table 2- 3 Baseline imaging characteristics in WW group vs. MV surgery and MV repair vs. MV replacement.

	Watchful Waiting n=15	**MV Surgery n=29**	**p-value**	**MV Repair n=16**	**MV Replacement n=13**	**p-value**
PCMR parameters						
LV end-diastolic volume (ml)	208±42	247±72	**0.03**	239±59	258±87	0.50
LV end-diastolic volume index (ml/m^2)	114±20	130±34	0.05	129±35	133±34	0.73
LV stroke volume (ml)	121±24	134±37	0.19	134±29	134±46	0.10
LV ejection fraction (%)	59±6	55±8	0.09	57±8	52±7	0.12
LV mass (g)	94±22	123±41	**0.004**	118±34	129±49	0.51
LV mass index (g/m^2)	51±11	64±16	**0.004**	63±15	66±19	0.67
RV end-diastolic volume (ml)	163(131-189)	177(160-217)	0.20	188±43	182±54	0.75

RV end-diastolic volume index (ml/m^2)	90(75-98)	97(83-111)	0.25	101±20	95±20	0.43
RV stroke volume (ml)	83(67-104)	81(67-107)	0.77	93(74-107)	74(66-107)	0.28
RV ejection fraction (%)	54±6	47±5	**0.001**	48±6	45±5	0.11
MR regurgitant volume (ml)	44±12	70±28	**<0.001**	64±20	76±35	0.30
MR regurgitant volume index (ml/m^2)	25±7	37±13	**<0.001**	35±12	39±14	0.39
MR regurgitant fraction (%)	34(29-46)	52(41-58)	**<0.001**	48±10	55±10	0.09
4DF-CMR parameters						
Mitral valve forward flow (ml)	134±32	142±45	0.49	146±41	137±51	0.62
Aortic valve stroke volume (ml)	75(61-82)	56(44-69)	**0.06**	55(45-75)	56(42-65)	0.32
MR regurgitant volume (ml)	63±26	83±41	**0.048**	83±34	83±49	0.98
MR regurgitant volume index (ml/m^2)	35±15	44±21	0.09	45± 20	43±24	0.84
MR regurgitant fraction (%)	47(37-57)	58(46-62)	**0.045**	54±13	55±17	0.95

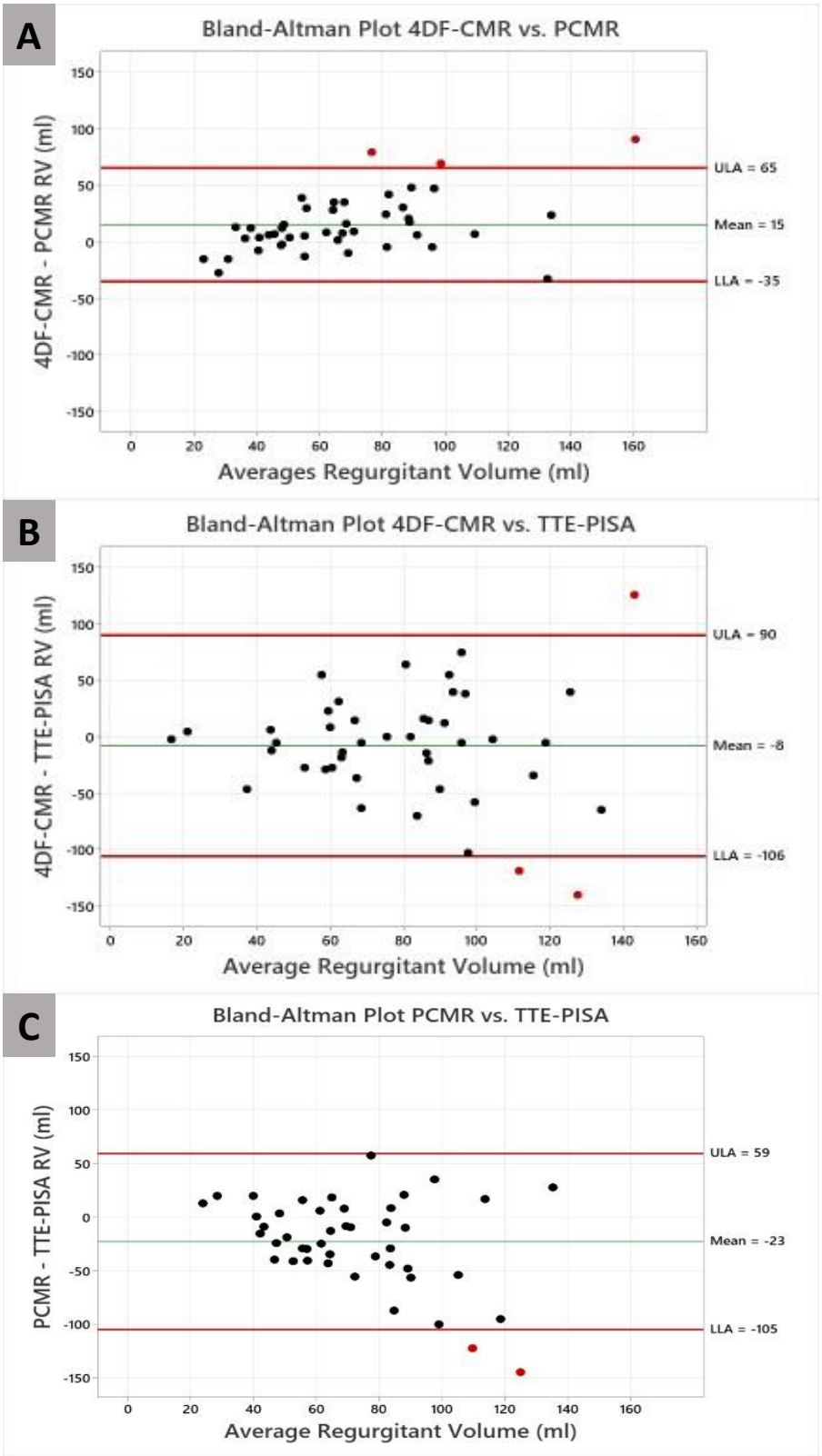
TTE parameters						
LV end-diastolic diameter – 2D (mm)	53±8	57±6	0.07	57±5	58±7	0.73
LV end-systolic diameter – 2D (mm)	34±6	39±7	**0.02**	39±6	40±7	0.71
LV ejection fractionTeicholz method (%)	63±8	59±9	0.13	60±9	57±8	0.51
MR regurgitant volume – PISA (ml)	67(47-85)	80(68-112)	**0.04**	103±44	78±30	0.08
MR regurgitant volume index (ml/m^2)	32(24-52)	44(36-55)	0.14	47(41-73)	41(34-48)	0.13
MR regurgitant fraction – PISA (%)	53±17	58±12	0.25	61±12	55±13	0.25
Vena contracta (cm)	0.5±0.1	0.6±0.2	0.46	0.6±0.2	0.5±0.2	0.26
PISA radius (cm)	0.9±0.2	1.0±0.2	0.24	1.1±0.2	1.0±0.3	0.43
EROA (cm^2)	0.46±0.19	0.60±0.25	0.06	0.65±0.25	0.53±0.25	0.20
Jet area/left atrium area (%)	42(37-49)	36(29-49)	0.07	37(31-61)	30(23-38)	0.14
E-wave velocity (m/s)	1.2±0.4	1.3±0.3	0.18	1.2±0.3	1.4±0.3	0.09

Data are presented as mean±SD and median(IQR1-IQR3). 2D=two-dimensional; CMR=cardiovascular magnetic resonance imaging; EROA=effective regurgitant orifice area; LV=left ventricle; MR=mitral regurgitation; MV=mitral valve; PISA=proximal isovelocity surface area; RV=right ventricle; TTE=transthoracic echocardiography; WW=watchful waiting.

All patients

The relationship between mitral regurgitant volume between the different modalities is demonstrated by Bland-Altman analysis in **Figure 2-3**. The bias was similar between all the modalities: 4DF-CMR and PCMR (15; 95% confidence interval [7,23]), 4DF-CMR and TTE (-8; 95% confidence interval [-23,7]), and PCMR and TTE (-23; 95% confidence interval [-39,-10]). While the limits of agreement were relatively wide between all modalities, they were narrower between 4DF-CMR and PCMR (-35ml-65ml), than between 4DF-CMR and TTE (-106ml-90ml), and between PCMR and TTE (-105ml-59ml).

Figure 2- 3 Bland-Altman plots.



Bland-Altman plots of the relationship between mitral regurgitant volume quantified by: panel (A) 4DF-CMR and PCMR, panel (B) 4DF-CMR and TTE-PISA and panel (C) PCMR and TTE-PISA. Green line represents bias, which is similar between all modalities: 4DF-CMR and PCMR (15), than

between 4DF-CMR and TTE-PISA (-8) and PCMR and TTE-PISA (-23). The limits of agreement, however, are narrower between 4DF-CMR and PCMR, than between the other modalities.

4DF-CMR=4D flow cardiovascular magnetic resonance imaging; LLA=lower limit of agreement; PCMR=phase-contrast magnetic resonance imaging; RV=regurgitant volume; TTE-PISA=transthoracic echocardiography-proximal isovelocity surface area method; ULA=upper limit of agreement**.**

2.4.3 Left and right ventricular reverse remodelling at 6-month follow-up

'Watchful Waiting' vs. MV Surgery

There were significant differences in the extent of reverse remodelling at 6-month follow-up between the WW group and patients who underwent MV surgery **(Table 2-4)**. Compared with WW group, patients in the MV surgery group had a significant reduction in LV end-diastolic volume (absolute, index and percentage), LV stroke volume and LV ejection fraction ($p<0.001$ for all). Left ventricular mass also significantly reduced in the MV surgery group (WW 2±8g vs. MV surgery -9±18g; $p=0.008$). With regards to the right ventricular parameters, there was a significant decrease in the right ventricular end-diastolic volume in patients who underwent MV surgery (WW 0±11ml vs. MV surgery -20±31ml; $p=0.003$).

MV Repair vs. MV Replacement

There were no significant differences in the amount of left and right ventricular reverse remodelling at 6 months between patients who underwent MVr and MVR **(Table 2-4)**. Although the reduction in the LV end-diastolic volume was numerically greater in the MVR group, this was not statistically significant ($p=0.18$).

Table 2- 4 Left and right ventricular reverse remodelling at 6 months by CMR.

Variable	**Watchful Waiting n=15**	**MV Surgery n=29**	**p-value**	**MV Repair n=16**	**MV Replacement n=13**	**p-value**
LV end-diastolic volume (ml)	-2±25	-61±44	**<0.001**	-51±33	-74±54	0.18
LV end-diastolic volume index (ml/m^2)	-1±12	-32±21	**<0.001**	-28±18	-38±23	0.24
LV end-diastolic volume (%)	-1±11	-24±14	**<0.001**	-22±13	-28±16	0.27
LV stroke volume (ml)	1±18	-55±30	**<0.001**	-52±24	-59±37	0.60
LV ejection fraction (%)	1±4	-11±10	**<0.001**	-11±7	-10±12	0.71
LV mass (g)	2±8	-9±18	**0.008**	-10±20	-7±16	0.72
LV mass index (g/m^2)	1±4	-5±10	**0.01**	-6±11	-4±8	0.53
LV mass (%)	3±18	-7±16	**0.007**	-8±17	-6±15	0.68
RV end-diastolic volume (ml)	0±11	-20±31	**0.003**	-21((-37)-(-9))	-10((-35)-7)	0.32

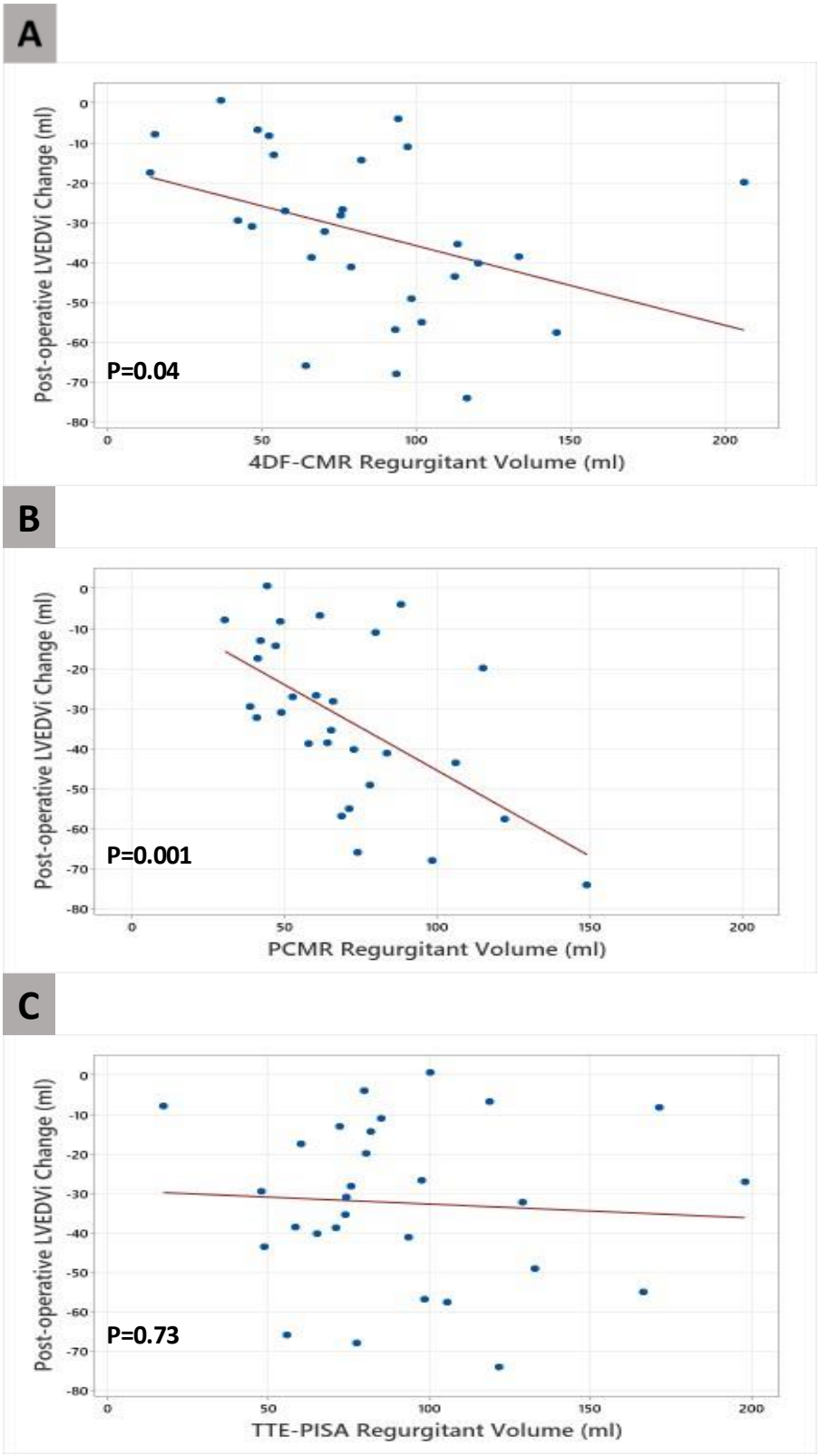
RV end-diastolic volume index (ml/m^2)	0±6	-10±14	**0.002**	-12±12	-8±17	0.51
RV stroke volume (ml)	-1±9	-7±20	0.24	-7((-19)-(-1))	-1((-9)-15)	0.054
RV ejection fraction (%)	0±4	1±8	0.33	0((-4)-5)	-3(0-8)	0.08

Data are presented as mean±SD and median(IQR1-IQR3). CMR=cardiovascular magnetic resonance imaging; LV=left ventricle; MV=mitral valve; RV=right ventricle.

Association of pre-operative MR volume and post-operative LV reverse remodelling

Results of the linear regression analysis between the post-operative change in left ventricular end-diastolic volume index and the pre-operative mitral regurgitant volume quantified by all modalities in the MV surgery group are shown in **Figure 2-4**. There was a significant association between the post-operative reduction in the LV end-diastolic volume index and the pre-operative MR-Rvol, when the MR-Rvol was quantified by 4DF-CMR (p=0.04) and by PCMR (p=0.001). There was no correlation when the MR-Rvol was quantified by the TTE (p=0.73). Furthermore, the receiver operator characteristic curves of MR-Rvol for post-operative reduction in LV end-diastolic volume index (more than mean volume of 32ml/m^2) demonstrated better performance by 4DF-CMR (area under the curve 0.83; p=0.04) and PCMR (area under the curve 0.78; p=0.03), than by TTE (area under the curve 0.51; p=0.89). **(Figure 2-5)**

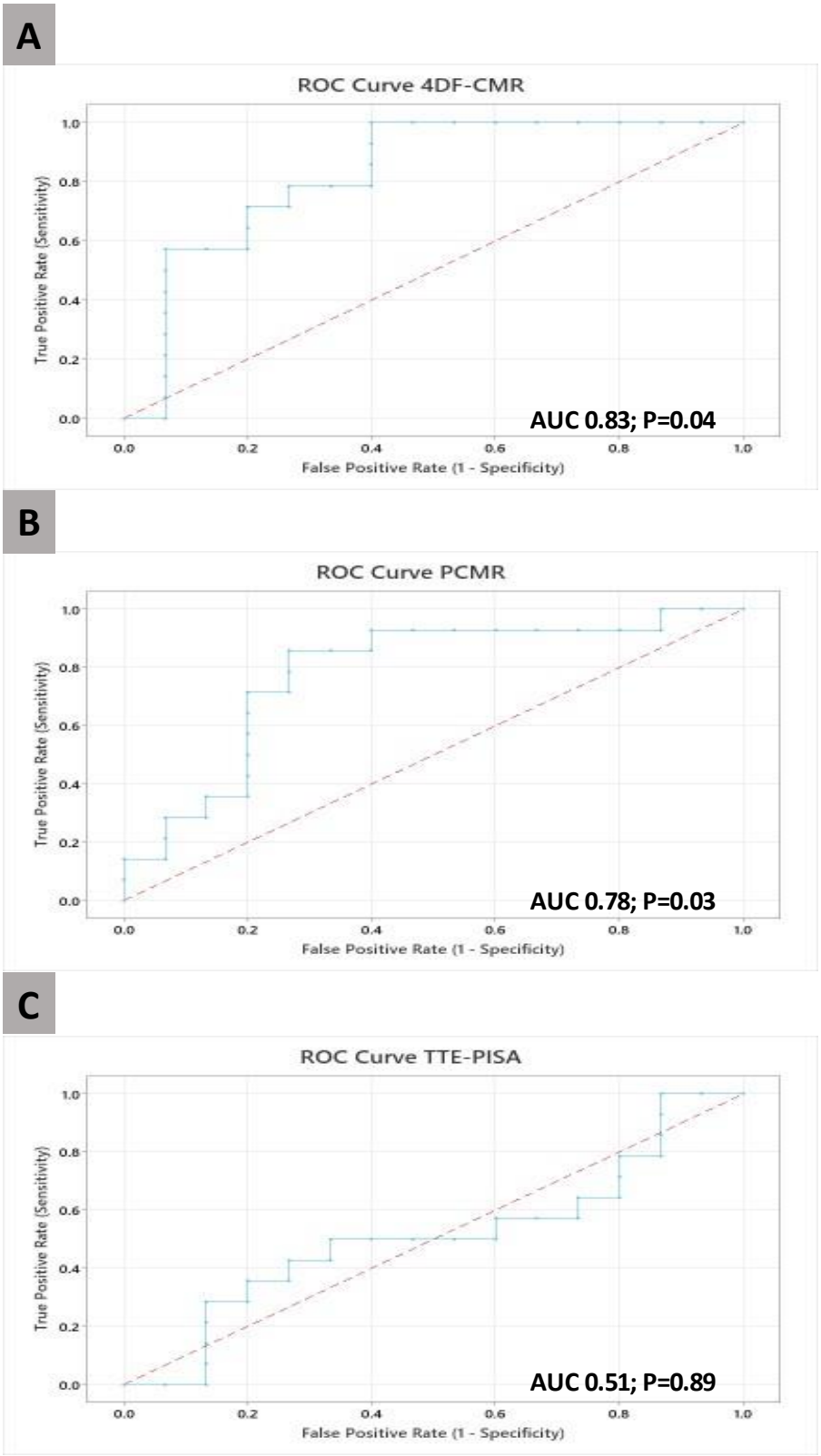
Figure 2- 4 Linear regression analysis between post-operative change in LV end-diastolic volume index and pre-operative MR-Rvol.



Panel (A) presents MR regurgitant volume quantified by 4DF-CMR, panel (B) by PCMR and panel (C) by the TTE-PISA method.

4DF-CMR=4D flow cardiovascular magnetic resonance imaging; LV=left ventricle; LVEDVi=left ventricular end-diastolic volume index; MR-Rvol=mitral regurgitant volume; PCMR=phase-contrast magnetic resonance imaging; TTE-PISA=transthoracic echocardiography-proximal isovelocity surface area method.

Figure 2- 5 Receiver operating characteristic curves.



ROC curves of mitral regurgitant volume for reduction of the left ventricular end-diastolic volume index (>mean of 32ml/m^2). In panel (A) mitral regurgitant volume was quantified by 4DF-CMR, in panel (B) by PCMR and in panel (C) by TTE-PISA. The area under the curve is greater with 4DF-

CMR (0.83; p=0.04) and PCMR (0.78; p=0.03), than with TTE (0.51; p=0.89).

4DF-CMR=4D flow cardiovascular magnetic resonance imaging; PCMR=phase-contrast magnetic resonance imaging; ROC=receiver operating characteristic; TTE-PISA =transthoracic echocardiography-proximal isovelocity surface area method.

2.4.4 Clinical outcomes and functional capacity

'Watchful Waiting' vs. MV Surgery

The mean duration of follow-up was similar in both groups **(Table 2-5)**. There were no significant differences between the rate of MACE composite or the individual MACE components between these groups. There was, however, a significant improvement in the 6MWT distance in the MV surgery group (WW 4±48m vs. MV surgery 55±60m; p=0.004).

MV Repair vs. MV Replacement

There were no significant differences in the rate of the MACE composite or the individual MACE components between the MVr and the MVR groups. The improvement in 6MWT distance was numerically, but not significantly, longer in the MVR group (MVr 38±47m vs. MVR 76±69m; p=0.11).

Table 2- 5 Comparison of outcomes between WW group vs. MV surgery and MV repair vs. MV replacement.

Variable	Watchful Waiting n=15	MV Surgery n=29	p-value	MV Repair n=16	MV Replacement n=13	p-value
Follow-up duration (months)	42.1±24.9	51.5±13.5	0.19	48.7±12.8	54.9±13.9	0.23
MACE, n(%)	5(33.3)	8(27.6)	0.74	5(31.3)	3(23.1)	0.70
Death, n(%)	2(13.3)	0(0.0)	0.11	0(0)	0(0)	-
Myocardial Infarction, n(%)	0(0)	0(0)	-	0(0)	0(0)	-
Stroke/TIA, n(%)	0(0.0)	3(10.3)	0.54	2(12.5)	1(7.7)	1
Hospitalisation due to HF, n(%)	2(13.3)	3(10.3)	1	1(6.3)	2(15.4)	0.57
Acute presentation due to arrhythmia, n(%)	2(13.3)	3(10.3)	1	2(12.5)	1(7.7)	1
Change in 6MWT distance at 6 months	4±48	55±60	**0.004**	38±47	76±69	0.11

Data are presented as mean±SD and n(%). HF=heart failure; MACE=Major Adverse Cardiovascular Events; MV=mitral valve; TIA=transient ischaemic attack; WW=watchful waiting; 6MWT=6-minute walking test.

2.4.5 Intra-observer reproducibility

The intra-observer reproducibility was excellent for the assessment of the mitral flow (ICC=0.980; 95% CI [0.917,0.995]), aortic flow (ICC=0.986; 95% CI [0.945,0.996]) and pulmonary flow (ICC=0.982; 95% CI [0.933,0.996]).

2.5 Discussion

To our knowledge, this is the first study to examine the relationship between 4DF-CMR-quantified pre-operative MR-Rvol and post-operative LV reverse remodelling. We have shown that not only the MR-Rvol quantified by 4DF-CMR is in close agreement with PCMR in primary MR, but also, that there is a significant association between the pre-operative 4DF-CMR-derived MR-Rvol and the post-operative reduction in the LV end-diastolic volume index. Furthermore, 4DF-CMR demonstrated better performance than PCMR and TTE for identifying a greater than the mean reduction in post-operative LV end-diastolic volume index. Finally, we have shown no difference in the degree of post-operative left ventricular reverse remodelling or the functional capacity and clinical outcomes between mitral valve repair and replacement.

2.5.1 Quantification of MR volume by 4DF-CMR, PCMR and TTE

While TTE is the first line imaging modality in mitral regurgitation, PCMR can be helpful in challenging cases, especially where the severity of MR remains uncertain.(98) Quantification of MR by TTE may be particularly difficult in primary MR, which is frequently complicated by late-systolic, multiple or eccentric jets, rendering the PISA method somewhat inaccurate.(56)

Although PCMR overcomes these limitations, 4DF-CMR has several advantages, making it potentially a very useful addition to the standard PCMR scan protocol. This novel technique is free breathing, requires only simple planning and enables direct assessment of flow across all four cardiac valves in one acquisition.(106)

Prior studies demonstrated, that 4DF-CMR is feasible and reproducible in MR.(23) Moreover, quantification of mitral valve flow by 4DF-CMR was accurate even in the presence of atrial fibrillation(99) and regardless of the scanner type and scan protocol(69). A study by Fidock et al showed that MR volume quantitated with 4DF-CMR utilising the indirect method, where 4DF-CMR-derived aortic stroke volume was subtracted from 4DF-CMR-dervied mitral forward flow, was comparable to the standard PCMR assessment, with a smaller absolute differences in the regurgitant volumes by these two methods than in our study; this method also had the highest reproducibility.(70) A number of other studies also showed that assessment of MR by 4DF-CMR is in agreement with PCMR.(9, 42) Different studies, however, have utilised various approaches for the assessment of agreement and correlation between these methods, therefore direct comparisons cannot be drawn between some of these studies and the current study.

While a study by Feneis et al demonstrated even narrower limits of agreement for the indirect approach (-13.13-14.24)(9), than our study, the limits of agreement in a study by Spampinato et al were similar (52.1-(-50))(42). The bias, however, was much smaller in the latter study (1.05±26.1).(42)

With regard to TTE, the results were somewhat variable, possibly owing to the different aetiologies of MR being evaluated. A recent study of patients with mitral valve prolapse found that TTE assessment yielded much larger regurgitant volumes than PCMR or 4DF-CMR(42), while regurgitant volumes were underestimated by TTE in functional MR(64). In our study, the limits of agreement were narrower between MR-Rvol assessed by 4DF-CMR and PCMR, than between 4DF-CMR and TTE or PCMR and TTE, while the mean bias was similar between all the modalities. It has been shown previously, that the TTE-PISA method in mitral valve prolapse may overestimate MR-Rvol, as the PISA radius is obtained from a single systolic frame, which may not accurately reflect the overall severity of MR. The presence of eccentric and multiple regurgitant jets can also render it inaccurate.(56) This may explain the results of our study.

2.5.2 Correlation of pre-operative MR regurgitant volume with post-operative LV reverse remodelling

The discordance in MR severity between PCMR and TTE has been shown in several studies.(55, 57, 107) Furthermore, studies showed that MR-Rvol assessed by PCMR had prognostic associations, while MR-Rvol assessed by TTE did not.(55-57) In asymptomatic patients, severe MR by PCMR was the best predictor of progression to surgery and all-cause mortality(57), whereas in the surgical cohort, there was a significant correlation between the PCMR-assessed MR severity with the post-operative reduction in the left ventricular end-diastolic volume(55, 107). No studies, however, have examined the relationship between 4DF-CMR-derived MR-Rvol and the

post-operative LV reverse remodelling. In our study, there was a significant association between the MR-Rvol assessed by 4DF-CMR and the post-operative reduction in the left ventricular end-diastolic volume index. Likewise, when the MR-Rvol was quantitated by PCMR, there was also a significant correlation with the post-operative LV reverse remodelling, in line with a previous study by Uretsky et al.(55) In line with the aforementioned studies, however there was no correlation between the TTE-derived MR-Rvol and the post-operative decrease in the LV end-diastolic volume index. This holds promise for the clinical applicability of 4DF-CMR in the assessment of primary MR.

Furthermore, the receiver operating characteristic analysis in this study showed that 4DF-CMR-derived MR-Rvol demonstrated the best diagnostic performance of all the techniques for identification of a more than mean reduction in the post-operative LV end-diastolic volume index. The diagnostic performance of PCMR-derived MR-Rvol was similar to that of 4DF-CMR MR-Rvol, whereas TTE demonstrated the smallest area under the ROC curve which was non-significant. Although no prior studies examined the diagnostic performance of 4DF-CMR-derived MR-Rvol in terms of post-operative LV reverse remodelling or clinical outcomes, the previous PCMR studies demonstrated good diagnostic performance of PCMR-derived MR-Rvol for the development of a surgical indication and for all-cause mortality(56, 57), while TTE showed much lower prognostic value(57). It is important to note, however that in accordance with the American Society of Echocardiography guidelines, a TTE-based assessment of MR severity should not rely on the regurgitant volume alone, but rather on a

comprehensive algorithm consisting of several variables.(100) In our study, regurgitant volume was used in isolation to enable direct comparison between the different modalities. Although this could potentially explain the low diagnostic performance of TTE, a recent study which compared the above algorithm with PCMR, found that despite using this integrated approach, only one half of the patients with severe MR by TTE, had severe MR by PCMR.(107)

As both, PCMR and 4DF-CMR-derived MR-Rvol in our study was obtained indirectly, errors due to multiple, eccentric and late-systolic jets, which are inherent in primary MR were potentially reduced. Although these indirect methods, which quantitate MR-Rvol by subtracting the aortic forward flow from the LV stroke volume in PCMR and aortic stroke volume from the mitral forward flow in 4DF-CMR are also bound by their own limitations, the indirect approach is the preferred PCMR method(100) and the most reproducible 4DF-CMR method(70). In summary, our study demonstrates the potential clinical utility of 4DF-CMR in assessment of primary MR, which can be either, an add on to a standard PCMR scan protocol to ensure consistency of results or an isolated approach in those unable to tolerate breath-holding or a full, standard PCMR scan protocol. Our study also indicated that TTE-derived MR-Rvol may need to be interpreted with caution in the setting of primary MR.

2.5.3 Left ventricular reverse remodelling and clinical outcomes in mitral valve repair vs. replacement

Current guidelines recommend mitral valve repair, rather than replacement if repair is feasible and likely to be durable.(1, 3) There are, however no randomised controlled trials to support this approach. While observational studies in primary MR suggest survival advantage in mitral valve repair(108, 109), the advancement of surgical techniques with the widespread use of chordal preservation techniques may improve the LV reverse remodelling following MVR(110). In our study, there were no significant differences in left and right ventricular reverse remodelling at 6-month follow-up. Interestingly, there was numerically, but not significantly, greater reduction in the LV end-diastolic volume in the MVR group. There was also no significant difference in the improvement in 6MWT distance between these two groups at 6-month follow-up. Furthermore, with regard to MACE, at a median follow up of 51.5±13.5months, there were no significant differences in the rate of MACE composite or the individual MACE components between MVr and MVR. As the follow-up duration in our study was relatively short, the long-term differences in the rate of MACE remain to be determined.

2.5.4 Limitations

This was a single-centre, prospective observational study and thus bound by limitations inherent in all observational studies. We recruited only stable patients undergoing elective surgery, who were able to undergo paired study assessments, therefore creating survivor bias. In terms of the echocardiographic evaluation, we only utilised the TTE-PISA method, which

is known to particularly problematic in primary MR.(56) Although this was a relatively small study, prior 4DF-CMR studies were similar in size. A large proportion of patients were unfortunately excluded due to death and patient's choice, but also due to suboptimal 4DF-CMR image quality and lack of a full 4DF-CMR dataset availability in some cases. Despite the above limitations, our study does add to the growing body of evidence that 4DF-CMR might be useful in assessment of primary MR in contemporary clinical practice.

2.6 Conclusions

To our knowledge, this is the first study that evaluated the relationship between the pre-operative MR-Rvol quantitated by 4DF-CMR and the post-operative LV reverse remodelling. Limits of agreement were much narrower between 4DF-CMR and PCMR, than between the other modalities. Similar to PCMR, there was a significant correlation between the pre-operative 4DF-CMR-derived MR-Rvol in primary MR and the post-operative reduction in the LV end-diastolic volume index, while there was no correlation when the MR-Rvol was assessed by TTE. Moreover, 4DF-CMR demonstrated best diagnostic performance of the three techniques. Although the results need to be verified in a larger study, they hold promise for the clinical utility of 4DF-CMR in the future assessment of primary MR.

Chapter 3
Mitral regurgitation assessment by cardiovascular magnetic resonance imaging during continuous in-scanner exercise: a feasibility study

3.1 Abstract

Background: In mitral regurgitation (MR), physiological exercise alters cardiac haemodynamics; however, exercise imaging using current modalities can be challenging. Biventricular function assessment has been shown to be feasible by exercise-cardiovascular magnetic resonance (EX-CMR) in healthy volunteers. Therefore, this was a patient focused study to establish the feasibility and reproducibility of EX-CMR acquired during continuous in-scanner exercise.

Methods: Asymptomatic patients with primary MR underwent biventricular volumes/function, aortic flow volume, MR volume (MR-Rvol) and regurgitant fraction (MR-RF) assessment at rest and during low- (Low-EX) and moderate-intensity exercise (Mod-EX).

Results: Twenty-five patients completed EX-CMR without complications. Whilst there were no significant changes in the left ventricular (LV) volumes, there was a significant increase in the LV ejection fraction (rest 63±5% vs. Mod-EX 68±6%;p=0.01). There was a significant reduction in the right ventricular (RV) end-systolic volume (rest 68ml(60-75) vs. Mod-EX 46ml(39-59);p<0.001) and a significant increase in the RV ejection fraction (rest 55±5% vs. Mod-EX 65±8%;p<0.001). Whilst overall, there were no

significant group changes in the MR-Rvol and MR-RF, individual responses were variable, with MR-Rvol increasing by ≥15ml in 4(16%) patients and decreasing by ≥15ml in 9(36%) of patients. The intra- and inter-observer reproducibility of LV volumes and aortic flow measurements were excellent, including at Mod-EX.

Conclusion: EX-CMR is feasible and reproducible in patients with primary MR. During exercise, there is an increase in the LV and RV ejection fraction, reduction in the RV end-systolic volume and a variable response of MR-Rvol and MR-RF. Understanding the individual variability in MR-Rvol and MR-RF during physiological exercise may be clinically important.

3.2 Introduction

In severe primary mitral regurgitation (MR), surgery is recommended in symptomatic patients or those with left ventricular (LV) dysfunction or dilated end-systolic cavity >45mm. In asymptomatic patients, who have high likelihood of successful repair and low operative mortality, mitral valve repair is also recommended in those with new-onset atrial fibrillation or pulmonary hypertension.(1) However, in some cases, irreversible LV remodelling may occur before the surgery. As such, appropriate timing of surgical intervention and identifying patients, who can potentially benefit from early surgery is crucial to prevent adverse outcomes and to improve prognosis.

Exercise testing plays an important role in patients with asymptomatic MR(1, 3), as about 20% of patients with no apparent symptoms have reduced functional capacity on a cardio-pulmonary exercise test (CPEX)(76). Other

currently available exercise testing modalities include treadmill test and exercise transthoracic echocardiography (EX-TTE), which can also provide useful insights into the left ventricular response to exercise and examine changes in MR during exercise.(1, 3) However, EX-TTE has several limitations, such as variable image quality and reproducibility, and can be very challenging due to motion artefact.(77)

Quantification of primary MR by cardiovascular magnetic resonance (CMR) imaging has been shown to have better prognostic association in asymptomatic MR than TTE.(56, 57) Moreover, CMR is the reference-standard for assessment of the LV and right-ventricular (RV) size and function.(14, 15) Exercise-CMR (EX-CMR) can, therefore, potentially overcome the limitations of EX-TTE and add diagnostic value in the assessment of asymptomatic patients with primary MR.

EX-CMR assessment of biventricular volumes has been shown to be feasible and reproducible in a small study of patients with primary MR.(77) Although in this study aortic flow measurements were not performed, which prevented assessment of MR severity and its response to exercise, we have also demonstrated the feasibility of bi-ventricular volumes and aortic flow assessment by EX-CMR in healthy volunteers.(82)

EX-CMR enables assessment of the effective forward ejection fraction, a novel concept that has been previously demonstrated in resting CMR and shown to correlate better with the post-operative LV ejection fraction (LVEF).(81) This, however, has never been assessed during physiological exercise in patients with primary MR. EX-CMR could, therefore, potentially

identify patients who would benefit from an early surgical referral as it may add diagnostic and prognostic information.

Therefore, we sought to demonstrate 1) the feasibility and reproducibility of EX-CMR assessment of biventricular volumes and aortic flow volume in patients with asymptomatic primary MR, during continuous supine in-scanner exercise, utilising vendor provided pulse sequences and standard analysis software; and 2) to describe the biventricular and MR regurgitant volume (MR-Rvol) and regurgitant fraction (MR-RF) changes that occur during exercise in this group of patients.

3.3 Methods

3.3.1 Study population

This was a prospective, single-centre feasibility study. We recruited patients with at least moderate primary mitral regurgitation, who were asymptomatic and had LVEF>55%. We excluded patients with a) secondary MR (atrial, ischaemic or rheumatic), b) indication for surgery as per the European Society of Cardiology guidelines(1): atrial fibrillation, evidence of pulmonary hypertension on TTE of ≥50mmHg or dilated LV cavity (LV end-systolic dimension ≥45mm), c) significant aortic valve disease on TTE (>mild), d) prior myocardial infarction, e) significant respiratory disease, f) contraindications to exercise stress testing(111) and g) general contraindications to CMR. Diagnosis of at least moderate MR was based on TTE criteria as per the American Society of Echocardiography

guidelines(112). The study was approved by the National Research Ethics Service (18/YH/0168), had institutional approval and complied with the Declaration of Helsinki. All patients provided written informed consent.

3.3.2 Exercise protocol

Patients exercised on a supine cycle ergometer (Lode BV, Netherlands) during the CMR scan. The exercise protocol used in this study was in accordance with the heart rate reserve (HRR) and an age predictive maximal heart rate model(113). In line with this model, an individual low (30-39% HRR) and moderate (40-59% HRR) exercise intensity was defined for each patient. The age-predictive maximal heart rate was calculated as per the following formula(113):

maximal heart rate=208 - 0.7 x age.

The low and moderate intensities were calculated as per the Karvonen method according to the following equation:

%HRR=((maximal heart rate−heart rate at rest) x % desired intensity of exercise) + HR rest.(114)

This method was used as it takes into account the lower resting and exercise heart rate, which occurs in supine position. Following resting imaging, patients exercised with no resistance (0 Watts) for 1 minute, with a

subsequent increase in the resistance by 25 Watts every 2 minutes and ideally 60-70 revolutions per minute. This was continued until the low intensity target heart rate was reached and stabilised for at least 30s, at which point CMR scanning was performed. When required, small increase in resistance were carried out to maintain the target heart rate. Once the low intensity stage was complete, further increase in resistance of 25 Watts every 2 minutes were undertaken until the moderate intensity target heart rate was reached and stabilised for at least 30s, whereupon further CMR scanning was performed. Patients exercised continuously with the CMR acquisition undertaken during exercise (rather than with exercise cessation), using a navigated free-breathing pulse sequence and with the receiver coil strapped to the patient to reduce motion artefact.

3.3.3 CMR protocol

A 1.5T Philips Ingenia (Best, The Netherlands) was used as previously validated in healthy volunteers in our centre(82). CMR scan protocol **(Figure 3-1)** included:

Imaging at rest

f) Survey images
g) Free-breathing transverse Half-Fourier Acquisition Single-shot Turbo spin Echo imaging
h) Cine images acquired with breath-hold balanced steady-state free precession sequence:
    a. 4-chamber view and vertical-long axis view
    b. 2 orthogonal left ventricular outflow tract views

c. Left ventricular short-axis stack. Sequence parameters: typical field-of-view 360mm, 10mm slice thickness with 0mm gap, repetition time 3.2ms, echo time 1.58ms, flip angle 60°, sensitivity encoding factor 2, 30 reconstructed phases, acquired matrix 192x132 and acquired voxel size 1.88x1.88mm.

i) Through-plane aortic phase contrast images (PCMR): planned at sino-tubular junction and orthogonal to the vessel.(40) Velocity encoding was set to 150cm/s. Sequence parameters: typical field-of-view 350x282mm, slice thickness 8mm, repetition time 4.9ms, echo time 2.9ms, flip angle 15°, number of signal averages 1, sensitivity encoding factor 2, 30 reconstructed phases, acquired matrix 140x113, acquired voxel size 2.5x2.5mm, Cartesian sampling, turbo field echo factor 3.

j) Compressed-SENSE (C-SENSE) protocol:

a. C-SENSE 3 left ventricular short-axis stack: free-breathing, respiratory navigated continuous imaging with C-SENSE acceleration - factor of 3. Imaging parameters: typical field-of-view 300x300mm, repetition time 2.4ms, echo time 1.2, flip angle 60°. Multishot turbo field echo factor 12, acquired heart phases 34, slice thickness 10mm, 0mm gap, acquired voxel size 2.5x3.45mm, acquired matrix 120x87.

b. C-SENSE 3 through-plane aortic phase contrast imaging stack: free-breathing, respiratory navigated continuous imaging with C-SENSE acceleration - factor of 3. Three 8mm overlapping slices were acquired with a -3mm gap to account for increased

motion during exercise, so that the centres of the individual slices were 5mm apart. Imaging parameters: typical field-of-view 350x320mm, repetition time 4.9ms, echo time 2.9ms, flip angle 15°, number of signal averages 1, turbo field echo factor 5, slice thickness 8mm, 30 reconstructed phases, acquired voxel size 2.5×2.5mm, acquired matrix 140x112, Cartesian sampling.

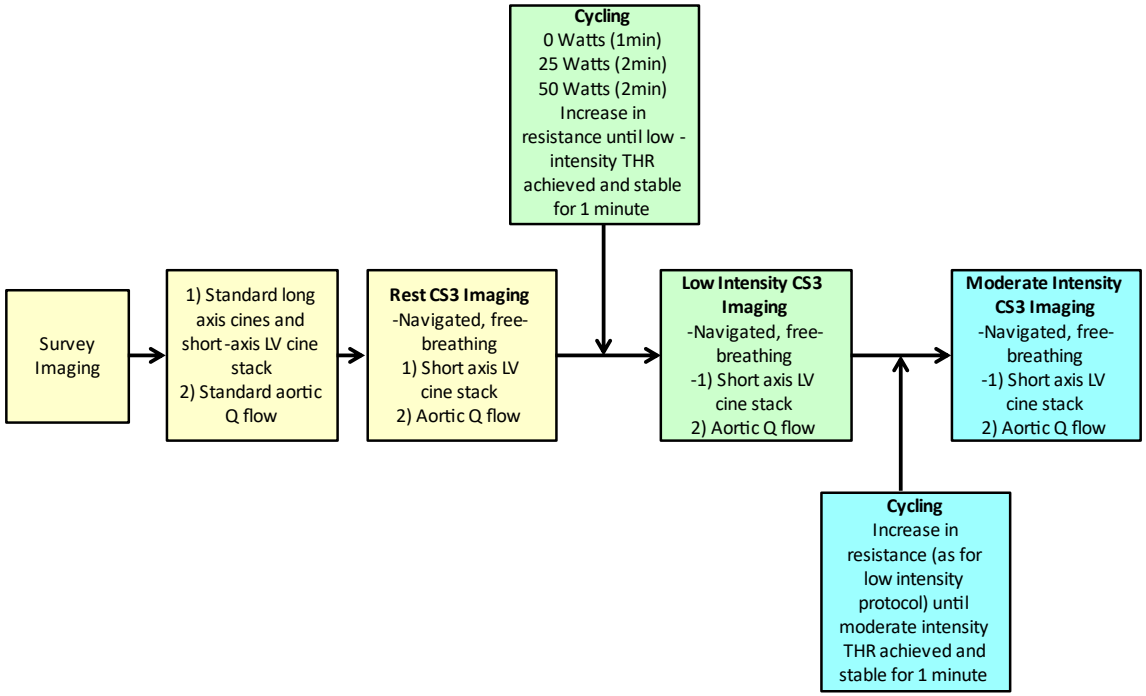
Low-intensity exercise (Low-EX) imaging

a) Free-breathing 4-chamber view and a left ventricular outflow tract view to allow re-planning of the short-axis cine imaging and phase-contrast imaging
b) C-SENSE 3 left ventricular short-axis stack: as per rest imaging
c) C-SENSE 3 through-plane aortic phase contrast imaging stack: as per rest imaging, except for velocity encoding, which was increased to 250cm/s

Moderate-intensity exercise (Mod-EX) imaging

a) As per low-intensity exercise imaging

Figure 3- 1 Exercise-CMR scan protocol.



CMR=cardiovascular magnetic resonance; CS3=compressed SENSE 3; LV=left ventricle; THR=target heart rate.

3.3.4 CMR image analysis

Analysis was performed by MG and TC using post-processing software (cvi42, Circle Cardiovascular Imaging, Calgary, AB, Canada). Blinded intra-observer analysis was performed by MG and blinded inter-observer analysis was performed by TC and NJ. Left and right ventricular volumes were obtained by manually tracing the endocardial border in end-diastole and end-systole, with trabeculations and papillary muscles being included in the blood pool. Final volumes were obtained by the summation of discs method.(115) Aortic flow was quantified by manually tracing the endovascular border in every cardiac phase. The slice closest to the sinotubular junction was chosen from the exercise PCMR stack for quantification of aortic flow at exercise to ensure consistency of results. Mitral regurgitant volume was obtained indirectly, by substracting aortic forward flow (AFF) volume from the LV stroke volume (LVSV). Mitral regurgitant fraction was obtained by dividing the MR-RVol by LVSV. Effective forward LVEF was calculated as follows: AFF/LVEDV as previously described.(81)

3.3.5 Statistical analysis

Continuous variables are presented as mean±SD or median with interquartile range as per normality of distribution. Normal distribution was determined by Anderson-Darling test. Categorical variables are expressed

as numbers and percentages. Continuous variables were compared by means of Student t-test (normal distribution) or Mann-Whitney test (non-normal distribution). The differences in continuous variables between rest, low- and moderate-intensity exercise were compared by repeated measures Analysis of Variance with Bonferroni correction for normally distributed variables and Friedman's test with Bonferroni correction (if significant) for non-normally distributed variables. Blinded intra-observer analysis was performed by MG and blinded inter-observer analysis by TC and NJ. The reproducibility was assessed by intra-class correlation with a two-way random model for absolute agreement and a 95% confidence interval. All analyses were performed using IBM SPSS (version 27) and statistical significance was defined as $P<0.05$.

3.4 Results

Twenty-nine patients were recruited to the study, of whom 4 were excluded from the final analysis (claustrophobia n=2, legs too long to use the ergometer n=1, severe artefact at low-intensity exercise n=1).

3.4.1 Demographic and clinical characteristics

Baseline demographic and clinical characteristics of the patient population are presented in **Table 3-1**. The majority of patients in our study were male (n=19;76%), with a median age of 65 years (55-69). The prevalence of co-morbidities was very low, with hypertension being the most common co-existing condition in 5 (20%) of patients. With regard to severity of MR,

almost half of the patients in our study had severe MR, with the remainder of patients having at least moderate MR. The most common aetiology was posterior mitral valve prolapse (n=15;60%).

Table 3- 1 Baseline patient characteristics.

Variable	**All patients n=25**
Age (years)	65(55-69)
Male, n(%)	19(76)
BMI (kg/m^2)	24±3
Weekly exercise (hours)	2(0-4)
Hypertension, n(%)	5(20)
Type 2 Diabetes Mellitus, n(%)	0(0)
Prior stroke/TIA, n(%)	1(4)
Prior MI, n(%)	0(0)
COPD, n(%)	0(0)
MR Severity as per TTE	
Severe	12(48)
Mod-severe	1(4)
Moderate	12(48)
MR Aetiology	
Posterior MVP, n(%)	15(60)

Anterior MVP, n(%)	0(0)
Bileaflet MVP, n(%)	9(36)
Mitral valve cleft, n(%)	1(4)

Data are presented as mean±SD, median(IQR1-IQR3) and n(%). BMI=body mass index; COPD=chronic obstructive pulmonary disease; MI=myocardial infarction; MR=mitral regurgitation; MVP=mitral valve prolapse; TIA=transient ischaemic attack; TTE=transthoracic echocardiography.

3.4.2 Haemodynamic and imaging characteristics at rest and during exercise

Haemodynamic characteristics

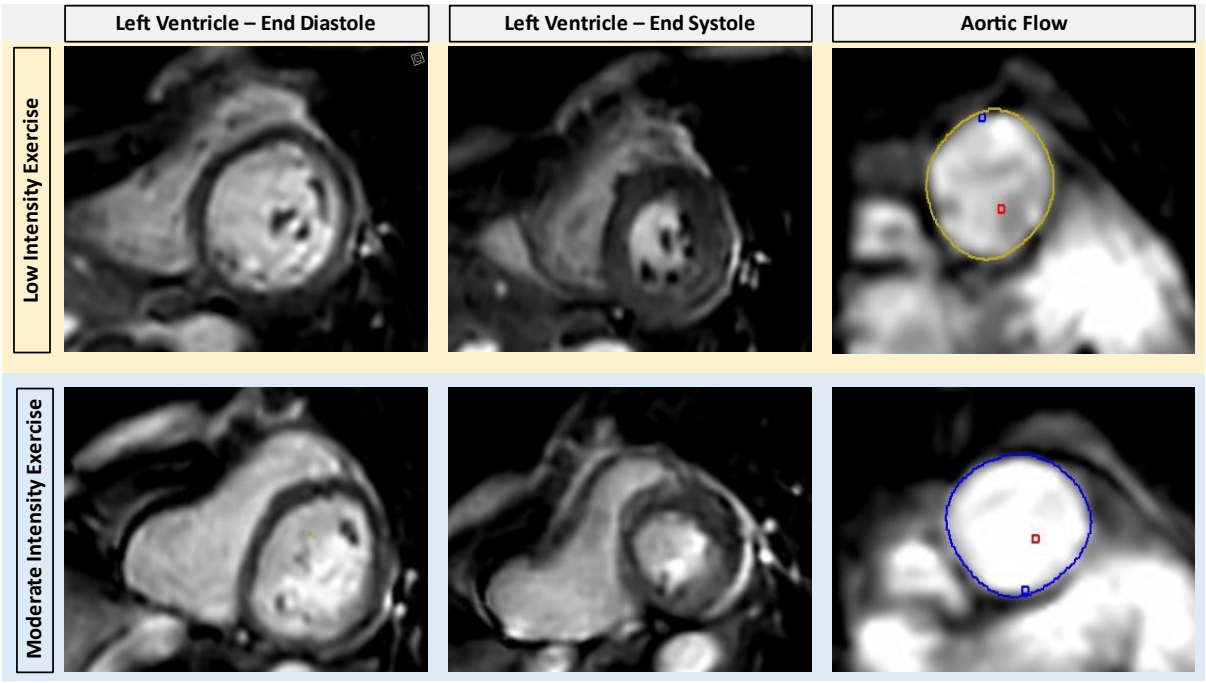
Both, heart rate and systolic blood pressure increased significantly during exercise **(Table 3-2).** The increase in heart rate was significant between all stages: rest vs. Low-EX ($p=0.001$), Rest vs. Mod-EX ($p<0.001$) and Low-EX vs. Mod-EX ($p=0.001$). The systolic blood pressure increased significantly between Rest vs. Low-EX ($p<0.001$) and Rest vs. Mod-EX ($p<0.001$), but not between Low-Ex and Mod-EX ($p=1.0$). There was no significant change in the diastolic blood pressure during exercise.

Imaging characteristics

An example of Ex-CMR image quality during Low-EX and Mod-EX is presented in **Figure 3-2**. The changes in the imaging parameters between rest, low-intensity exercise and moderate-intensity exercise are presented in **Table 3-2**. With regard to the changes in the left ventricular parameters, there were no significant changes in the LV end-diastolic volume, end-diastolic volume index or stroke volume during exercise. Although, the LV

end-systolic volume reduced numerically, especially between rest and Low-EX, this was not statistically significant (p=0.11). The LVEF, however, increased significantly between Rest vs. Low-EX (63%±5 vs. 68%±5, respectively; p=0.01), with no further increase between Low-EX vs. Mod-EX (68%±5 vs. 68%±6, respectively; p=1.0).

Figure 3- 2 An example of exercise-CMR image quality at low-intensity and moderate-intensity exercise.



CMR=cardiovascular magnetic resonance.

Similar to the left ventricular parameters, there were no significant changes in the RV end-diastolic volume, end-diastolic volume index or the stroke volume. The RV end-systolic volume, however, reduced significantly during exercise (rest 68ml(60-75) vs. Mod-EX 46ml(39-59); p<0.001). The RV ejection fraction also increased significantly between Rest to Mod-EX stage of exercise (55%±5 vs. 65%±8, respectively; p<0.001).

With regard to the LV contractile reserve, 14 patients (56%) demonstrated LVEF increase of at least 4% at Low-EX, while 15 patients (60%) demonstrated LV contractile reserve at Mod-EX. There were 4 patients (16%), who did not have LV contractile reserve at Low-EX, but had an increase in LVEF of more than 4% in the Mod-EX stage. There were 3 patients (12%), who demonstrated LV contractile reserve at Low-EX, but subsequently had a decrease in the LVEF in the Mod-EX stage.

While there were no significant changes in the LVEDV and the AFF, the effective forward LVEF increased significantly between Rest vs. Mod-EX (39%±8 vs. 47%±10, respectively; p=0.01), but not between rest and Low-EX stage of exercise (p=0.20) or between Low-EX and Mod-EX stage (p=0.76).

Table 3- 2 Comparison of haemodynamic and CMR parameters at rest, low-intensity and moderate-intensity exercise.

	Rest	**Low-intensity exercise**	**Moderate-intensity exercise**	**p-value**	**Rest vs. Low-Intensity**	**Rest Vs. Moderate-Intensity**	**Low vs. Mod-Intensity**
Haemodynamic parameters							
HR achieved (bpm)	63(59-68)	98(95-105)	112(109-118)	**<0.001**	**0.001**	**<0.001**	**0.001**
Systolic BP (mmHg)	130(121-138)	142(137-161)	159(138-170)	**<0.001**	**<0.001**	**<0.001**	1.0
Diastolic BP (mmHg)	78±8	79±19	78±13	0.91	-	-	-
Cycle resistance (W)	-	50(50-60)	75(55-75)	**<0.001**	-	-	**<0.001**
CMR parameters							
LV EDV (ml)	201±41	201±41	193±39	0.69	-	-	-

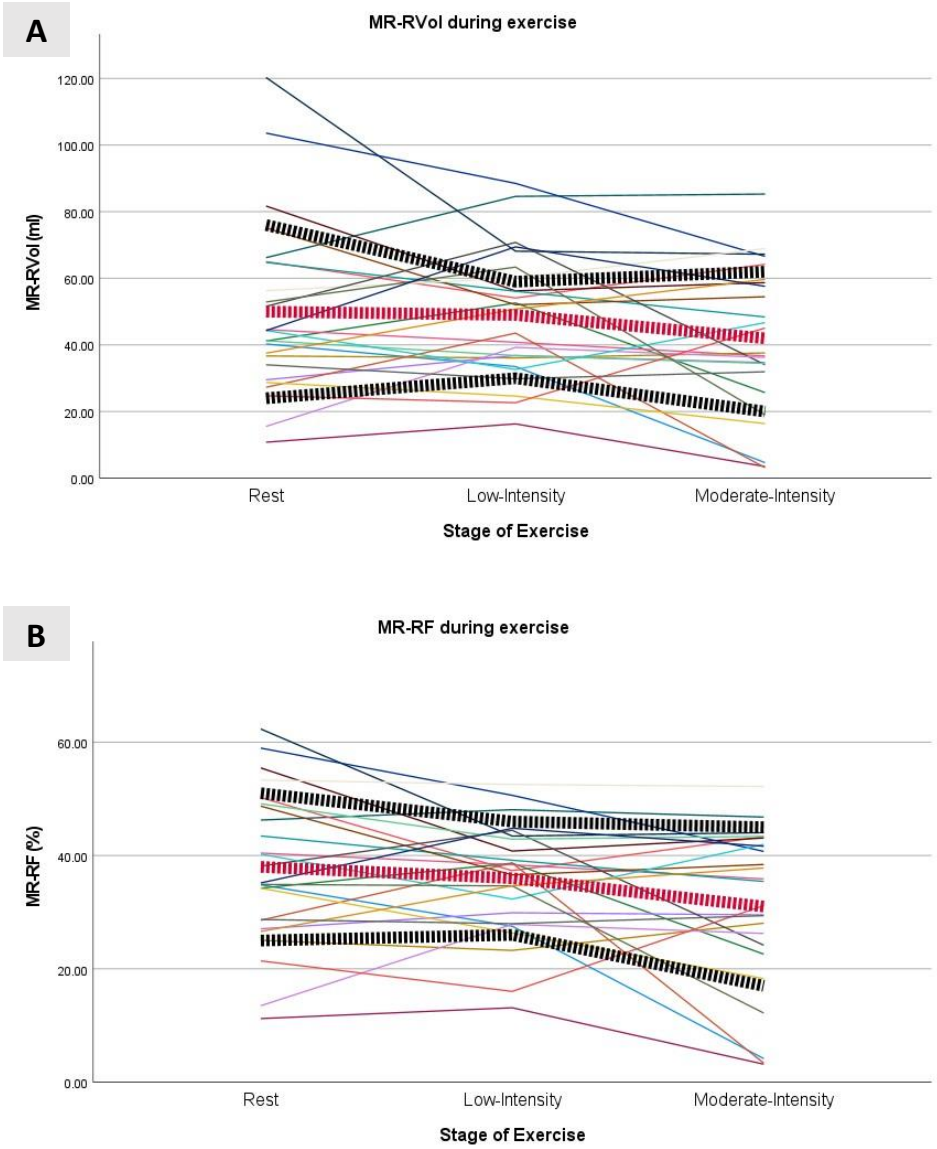
LV EDV index (ml/m^2)	108±19	108±18	104±19	0.63	-	-	-
LV ESV (ml)	74±20	65±20	63±20	0.11	-	-	-
LV SV (ml)	127±27	135±26	130±25	0.51	-	-	-
LV EF (%)	63±5	68±5	68±6	**0.004**	**0.01**	**0.01**	1.0
RV EDV (ml)	151±29	151±28	145±31	0.68	-	-	-
RV EDV index (ml/m^2)	81±15	81±13	78±16	0.62	-	-	-
RV ESV (ml)	68(60-75)	57(47-71)	46(39-59)	**<0.001**	0.10	**<0.001**	**0.03**
RV SV (ml)	84±19	92±25	95±26	0.21	-	-	-
RV EF (%)	55±5	61±9	65±8	**<0.001**	0.06	**<0.001**	0.17
Aortic forward flow (ml)	77±16	86±18	88±19	0.08	-	-	-
Effective forward LVEF(%)	39±8	44±8	47±10	**0.01**	0.20	**0.01**	0.76

MR-Rvol (ml)	50±26	49±19	42±22	0.39	-	-	-
MR-RF (%)	35(29-49)	37(28-43)	35(23-43)	0.18	-	-	-
Number of patients with LV contractile reserve, n(%)	-	14(56)	15(60)	-	-	-	-
Number of patients with an increase in MR-Rvol ≥15ml, n(%)	-	5(20)	4(16)	-	-	-	-
Number of patients with a decrease in MR-Rvol ≥15ml, n(%)	-	4(16)	9(36)	-	-	-	-

Data are presented as mean±SD and median(IQR1-IQR3). BP=blood pressure; CMR=cardiovascular magnetic resonance; EDV=end-diastolic volume; EF=ejection fraction; ESV=end-systolic volume; HR=heart rate; LV=left ventricle; MR-Rvol=mitral regurgitant volume; MR-RF=mitral regurgitant fraction; RV=right ventricle; SV=stroke volume.

There were no statistically significant changes in the MR-Rvol and MR-RF during exercise, although the MR-Rvol reduced numerically between Rest and Mod-EX stage (50ml±26 vs. 42ml±22, respectively; p=0.39). While overall, there were no significant changes in the MR-Rvol and MR-RF in this group, the individual response to exercise was quite variable. **(Figure 3-3)** Mitral regurgitant volume increased by more than 15ml from rest to Low-EX in 5(20%) patients and from rest to Mod-EX in 4(16%) patients. There was, however, reduction in severity of MR in 4(16%) patients at Low-EX and in 9(36%) patients at Mod-EX.

Figure 3- 3 Individual and group changes in MR-Rvol and MR-RF during exercise-CMR.



Panel (A) presents individual responses of MR-Rvol during exercise in all patients. Dashed red line represents the mean and the black dashed lines represent the standard deviation. Panel (B) presents individual responses of MR-RF during exercise in all patients. Dashed red line represents the mean and the black dashed lines represent the standard deviation. MR-Rvol=mitral regurgitant volume; MR-RF=mitral regurgitant fraction.

3.4.3 Intra- and inter-observer reproducibility

The intra-class correlation co-efficient and 95% confidence intervals for the intra- and inter-observer reproducibility of imaging parameters at rest, low-intensity and moderate-intensity exercise are presented in **Table 3-3**.

Intra-observer reproducibility

The intra-observer reproducibility was excellent for all imaging parameters at rest and at low-intensity exercise. At moderate-intensity exercise, it was excellent for all parameters, except the RV end-systolic volume, where it was good.

Inter-observer reproducibility

At rest, the inter-observer reproducibility was excellent for LV parameters and aortic forward flow, whereas it was moderate-to-good for right-ventricular parameters. At low-intensity exercise, it remained good-to-excellent for left ventricular parameters, AFF and RV end-diastolic volume, whereas it was poor for the assessment of RV end-systolic volume. At moderate-intensity exercise, it was good-to-excellent for all parameters, except RV end-systolic volume, for which it was moderate.

Table 3- 3 Intra- and inter-observer reproducibility.

		Intra-observer		Inter-observer	
Stage	**Parameter**	**ICC**	**95% CI [lower, upper]**	**ICC**	**95% CI [lower, upper]**
Rest	LVEDV	0.997	[0.989,0.999]	0.992	[0.971,0.998]
	LVESV	0.993	[0.975,0.998]	0.977	[0.912,0.994]
	RVEDV	0.997	[0.987,0.999]	0.866	[0.480,0.966]
	RVESV	0.986	[0.941,0.997]	0.681	[-.086,0.917]
	AFF	0.995	[0.980,0.999]	0.989	[0.955,0.997]
Low-Intensity	LVEDV	0.993	[0.971,0.998]	0.945	[0.791,0.986]
	LVESV	0.994	[0.927,0.999]	0.815	[0.228,0.954]
	RVEDV	0.985	[0.943,0.996]	0.837	[0.312,0.960]

	RVESV	0.992	[0.959,0.998]	-.319	[-3.461,0.656]
	AFF	0.995	[0.960,0.999]	0.971	[0.878,0.993]
Moderate-Intensity	LVEDV	0.989	[0.950,0.997]	0.984	[0.937,0.996]
	LVESV	0.992	[0.967,0.998]	0.916	[0.680,0.979]
	RVEDV	0.993	[0.914,0.999]	0.833	[0.366,0.958]
	RVESV	0.885	[0.559,0.971]	0.575	[-.329,0.886]
	AFF	0.996	[0.981,0.999]	0.954	[0.804,0.989]

AFF=aortic forward flow; CI=confidence interval; ICC=Intraclass Correlation Coefficient; LVEDV=left ventricular end-diastolic volume; LVESV= left ventricular end-systolic volume; RVEDV=right ventricular end-diastolic volume; RVESV= right ventricular end-systolic volume.

3.5 Discussion

To our knowledge, this is the first study that allowed assessment of biventricular volume and function as well as quantification of MR during continuous supine EX-CMR in asymptomatic patients with primary MR. We have demonstrated not only that continuous supine EX-CMR with the use of C-SENSE is feasible in asymptomatic patients with primary MR, but also that there was good-to-excellent reproducibility for quantification of the left ventricular volumes and aortic forward flow at low- and moderate-intensity exercise. We have also described the changes that occur in LV/RV volume and function, aortic forward flow, effective forward LVEF and MR-Rvol and MR-RF during supine in-scanner exercise. We have shown that while there was a significant augmentation of the LV and RV ejection fraction as well as the effective forward LVEF during exercise, there were no statistically significant changes in the MR-Rvol and MR-RF, although the individual responses were quite variable.

3.5.1 Feasibility of EX-CMR in asymptomatic patients with primary MR

Although EX-CMR is not commonly utilised, as it is constrained by technical challenges and the availability of expensive exercise equipment(78), it offers several advantages over EX-TTE(77). Not only does exercise testing enable the assessment of symptoms(76), but EX-TTE has been shown to provide

valuable information with regard to the LV and RV function and can demonstrate increasing severity of MR during exercise(116), therefore adding useful diagnostic and prognostic information. The added advantages of EX-CMR include superior image quality and reproducibility(77). A small study by Chew et all demonstrated the clinical feasibility of biventricular volume assessment during continuous in-scanner exercise in patients with MR.(77) Subsequently, the feasibility of biventricular volume and aortic flow quantification with the use of C-SENSE pulse sequences during continuous supine in-scanner exercise has been demonstrated by Craven et al in healthy volunteers.(82) Utilising the above C-SENSE pulse sequence to examine both, biventricular volumes and aortic flow during continuous in-scanner exercise, we have demonstrated its feasibility in asymptomatic patients with primary MR. All patients in our study, who were able to proceed with the EX-CMR scan, completed the examination in its entirety without complications.

3.5.2 Reproducibility

Similar to the aforementioned study in healthy volunteers(82), we have demonstrated excellent reproducibility for the assessment of LV end-diastolic volume and aortic forward flow at both, low- and moderate-intensity exercise. In this study, the LV end-systolic volume reproducibility at low-intensity exercise was good, whereas it was excellent at moderate-intensity exercise. This is reassuring, as standard quantification of MR is based on LV end-diastolic volume, LV end-systolic volume and aortic forward flow volume. This holds even more promise for the clinical utility of the effective

forward LVEF, which relies solely on the LV end-diastolic volume and aortic forward flow volume, both of which had an excellent intra- and inter-observer reproducibility, even at moderate-intensity exercise.

3.5.3 Left ventricular volume and function during exercise

A meta-analysis of supine EX-CMR studies in healthy volunteers, demonstrated that the physiological response to exercise consisted of an increase in heart rate and LV stroke volume, which occurred as a result of reduction in the LV end-systolic volume with no change in the LV end-diastolic volume.(79) A small supine EX-CMR study, which evaluated 5 patients with severe MR found, similar to our study, a significant increase in the heart rate, no change in the LV end-diastolic volume, non-significant reduction in the LV end-systolic volume and a significant increase in the LVEF.(77) As this is the only prior study, which utilised EX-CMR in patients with primary MR, the majority of current evidence stems from studies in exercise echocardiography. In these studies, however, exercise was performed in an upright or semi-supine position rather than fully supine.(117-120) This is important, as the haemodynamic response to exercise differs, depending on the patient's position.(121) These aforementioned studies mostly demonstrated reduction in the LVEDV during exercise.(119, 120)

Furthermore, exercise imaging enables assessment of LV contractile reserve(122), which is defined as the ability to augment LVEF during exercise by more than 4%; lack of contractile reserve has been shown to be associated with LVEF impairment following mitral valve intervention as well as worsening of LVEF in those undergoing medical management.(123) As

CMR is the reference-standard for assessment of left ventricular volume and function at rest(124), EX-CMR has the potential for accurate measurement of LV contractile reserve in this group of patients. In our study, more than half of the patients demonstrated contractile reserve at both, low- and moderate-intensity exercise. In some patients, however, while the contractile reserve was present at Low-EX, it was absent at Mod-EX, and vice versa. Future EX-CMR studies should aim to correlate not only the absence of the contractile reserve with clinical outcomes, but also evaluate the clinical significance of such a variable response in patients with primary MR.

3.5.4 Right ventricular volume and function during exercise

In asymptomatic patients with primary MR, the development of RV dysfunction during exercise showed prognostic associations in an EX-TTE study.(125) As assessment of RV size and function by TTE is difficult even at rest, reduction in tricuspid excursion can be utilised as a marker of RV dysfunction, at rest and during exercise.(125) In contrast to TTE, CMR can provide direct, accurate and reproducible measurements of RV volumes and function at rest(15). This high level of accuracy and reproducibility at rest holds promise for the clinical utility of RV volume and function assessment during exercise. Indeed, an EX-CMR study in healthy volunteers demonstrated good-to-excellent intra- and inter-observer reproducibility for the assessment of the RV end-diastolic and end-systolic volume. This study showed, that in healthy volunteers, there was reduction of the RV end-diastolic volume, marked reduction in the end-systolic volume and a significant increase in the RV ejection fraction during exercise.(82) The only

previous EX-CMR study in patients with asymptomatic, severe MR also demonstrated significant reduction in the RV end-systolic volume, but with no change in the RV end-diastolic volume and a non-significant increase in the RV ejection fraction.(77) While there was no significant change in the RV end-diastolic volume in our study, there was a significant decrease in the RV end-systolic volume, leading to a significant improvement in the RV ejection fraction. In our study, however, one half of the patients had moderate MR only, which may explain the more pronounced increase in the RV ejection fraction. Although our study did not look at clinical outcomes, prior EX-CMR studies in other conditions demonstrated the clinical utility of RV assessment by CMR during exercise.(126, 127) Future studies should therefore focus on correlating RV volume and function changes during exercise with clinical outcomes.

3.5.5 Mitral regurgitant volume and fraction during exercise

As the only prior EX-CMR study in primary MR did not assess aortic flow, it could not accurately quantify changes in MR regurgitant volume and regurgitant fraction during exercise.(77) In our study, while overall there was no significant change in these parameters, the individual response to exercise was quite variable. This is in line with prior studies, which demonstrated variable responses, with MR-Rvol increasing in about a third of patients. Furthermore, increase in MR-Rvol by more than 15ml during exercise was associated with reduced symptom-free survival.(118) This increase in severity during exercise is possibly related to the absence of the

LV contractile reserve(128), which may also be responsible for the diminished functional capacity in these patients(129).

3.5.6 Effective forward left ventricular ejection fraction

Current guidelines recommend mitral valve intervention in asymptomatic patients with severe MR in the presence of reduced LV ejection fraction or increased LV end-systolic diameter, amongst others.(1) However, once LV dysfunction ensues, it may be irreversible. It is therefore crucial to detect subclinical LV impairment, which may be present despite normal LV ejection fraction.(80, 130) Effective forward LV ejection fraction has been proposed as a superior measure to predict outcomes and guide surgical intervention in this group of patients.(130) Significant impairment of effective forward LVEF prior to mitral valve surgery has been shown to be associated with post-operative LV dysfunction.(81) It may therefore provide means of accurate assessment of the actual LV function in patients with MR. While the above studies demonstrated the prognostic advantage of the effective forward LVEF assessment at rest, the response to exercise and its clinical significance have not been previously described. In the current study, there was a significant increase in the effective forward LVEF at moderate-intensity exercise, despite non-significant changes in the aortic forward flow and LV end-diastolic volume. The standard LVEF has also increased during exercise in this study, however we did include patients with moderate as well as severe MR. Therefore, larger studies are needed to evaluate whether there is discordance between standard LVEF and the effective forward LVEF in certain cases and demonstrate its possible clinical significance.

3.5.7 Future perspectives

This study demonstrated the feasibility and reproducibility of EX-CMR for biventricular and mitral regurgitation assessment in asymptomatic patients with primary MR. The study utilised commercially available cycle ergometer and pulse sequences as well as standard commercially available analysis software, without the need for complex post-processing. Although TTE is the first-line modality in the assessment of MR(1), the new evidence becoming available suggests that conventional, resting TTE may be insufficient in certain cases, especially when surgery is being considered for prognostic reasons in the asymptomatic patients(3). While EX-TTE provides additional diagnostic and prognostic information, it is bound by standard TTE limitations, which become even more pronounced during exercise(77). Indeed, one EX-TTE study showed that it was not feasible to assess MR severity in almost half of the patients, and it was particularly challenging in those with MV prolapse.(131) As CMR is the reference-standard for biventricular volume/function assessment(15, 60) and has been shown to have prognostic associations in primary MR(57), EX-CMR hold promise as the exercise imaging modality of choice in this group of patients.

3.5.8 Limitations

This was a small, single-centre, feasibility study. All recruited patients were clinically well, able to exercise and did not have any significant co-existing

conditions. EX-CMR may therefore be less well tolerated or even not possible in symptomatic patients or those with other co-morbidities, such as respiratory disease or arthritis. We did, however, aim to evaluate the feasibility of EX-CMR in asymptomatic patients with primary MR, in whom it could theoretically assist in guiding surgical therapy decisions. All patients were in normal sinus rhythm, as the presence of atrial fibrillation was an exclusion criterion due to it being an indication for surgery. Presence of an arrhythmia could potentially lead to a significant reduction in image quality, in addition to motion artefact. While increased abdominal girth may be a problem for a standard, resting CMR, EX-CMR is further limited by patient's height, as very tall patients may not be able to cycle within the bore. Although the exclusion criteria were quite strict, this was still a very heterogenous group of patients as the patients with moderate MR may stay asymptomatic for decades, while some of the patients with severe MR may have met criteria for surgical intervention shortly after the study visit. Therefore, the response to EX-CMR in these patients might have been very different. Lastly, as this was a feasibility study, clinical outcomes were not assessed, and prognostic information cannot be derived from this study.

3.6 Conclusions

In this pilot study, we demonstrated the feasibility of performing CMR imaging during continuous, supine, in-scanner exercise in asymptomatic patients with moderate and severe MR. We have also shown that the assessment of biventricular volumes and quantification of MR during exercise in this group of patients is not only feasible, but also reproducible, even at moderate-intensity exercise. We have also described that changes that occur in the biventricular volumes during exercise and demonstrated the dynamic and variable response of MR severity. Future studies are needed to correlate these changes with clinical outcomes.

Chapter 4
Four-dimensional flow CMR during continuous in-scanner exercise: pulse sequence development and feasibility study

4.1 Abstract

Introduction: Four-dimensional flow cardiovascular magnetic resonance imaging (4DF-CMR) offers several advantages in the assessment of valvular heart disease. It has been shown to be accurate and reproducible; it does not require breath-holding and the acquisition time is much shorter than that of a standard CMR protocol. While 4DF-CMR is an accurate and feasible alternative to standard CMR assessment, exercise-imaging can add further diagnostic and prognostic information in valvular heart disease, especially in primary mitral regurgitation (MR). Combining these two techniques can, therefore, potentially offer several advantages in the assessment of MR. A clinically applicable 4DF-CMR pulse sequence that works during exercise, however, has not yet been developed. Therefore, we aimed to try to optimise a clinically available 4DF-CMR pulse sequence for acquisition of 4DF-CMR during moderate-intensity exercise.

Methods: In the first part of the pulse sequence development (PSD), we attempted to acquire diagnostic 4DF data during continuous in-scanner cycling in healthy volunteers by optimising R-R interval, changing voxel size, temporal resolution, resistance, denoising and k-space order. Once reasonable images were obtained, the final parameters were used to acquire 4DF-CMR data during exercise in 10 healthy volunteers.

Results: During PSD we established, that the best pulse sequence parameters were: temporal resolution of 40ms and isotropic voxel size of 3mm, VENC of 300cm/s, strong denoising, non-linear stretching, higher resistance, C-SENSE factor of 9, radial CENTRA' k-space order and exercise for 16% of the total estimated 4DF-CMR acquisition time. Ten volunteers participated in the feasibility assessment part of the study; mean age 45±7 years, male n=8(80%). Other than one volunteer, who had excellent quality images with no aliasing, most of the 4DF images were either poor or non-diagnostic, and severely degraded by aliasing.

Discussion: While we were not able to develop a successful, clinically applicable 4DF-CMR pulse sequence for acquisition during exercise, we have been able to acquire 4DF images at moderate-intensity heart rates and we were able to optimise the pulse sequence, so that excellent quality images were obtained in one volunteer.

Conclusions: Further adjustments are needed to develop a clinically applicable 4DF-CMR in exercise pulse sequence, which potentially could have diagnostic and prognostic advantages in the assessment of valvular heart disease.

4.2 Introduction

Four-dimensional flow CMR (4DF-CMR) enables assessment of all four cardiac valves within a single acquisition. Quantification of transvalvular flow by 4DF-CMR has been shown to be accurate and reproducible. Furthermore, internal validation of measurements is possible due to conservation-of-mass principle.(16, 22-24) The 4DF-CMR acquisition is also

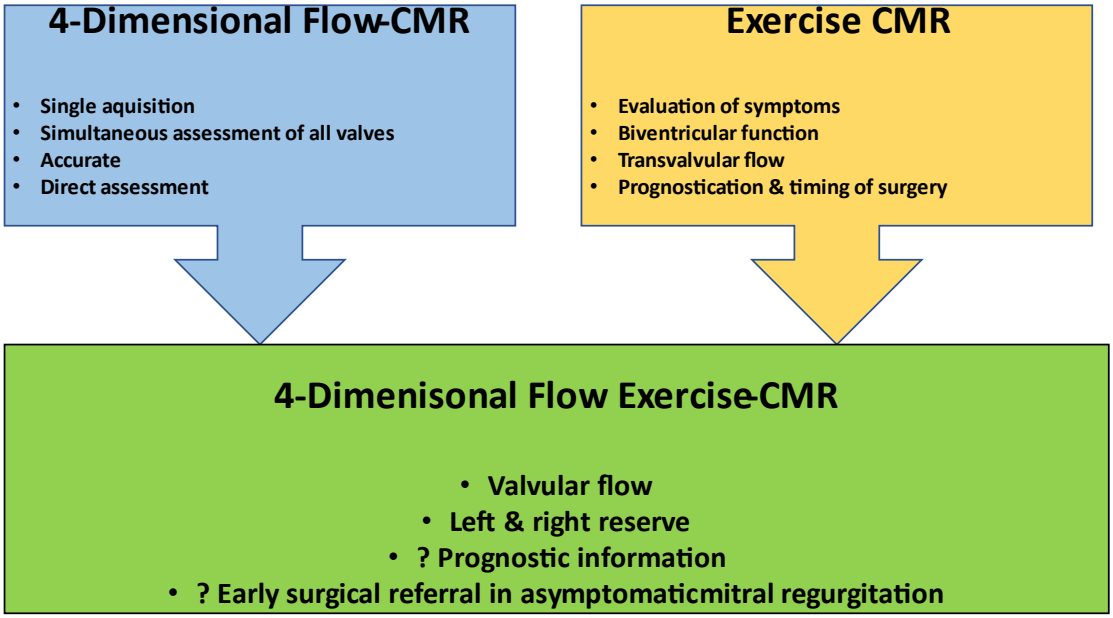
free-breathing and takes significantly less time than a whole standard CMR protocol.(106) It, therefore, offers several advantages in the assessment of valvular heart disease and can be utilised either as an add-on to the standard CMR protocol or used alone in patients unable to tolerate a prolonged scan or breath-holding.

Exercise imaging, such as exercise-transthoracic echocardiography (EX-TTE) enables evaluation of not only symptoms, but also biventricular and valvular flow changes during exercise.(132) Assessment by EX-TTE, particularly in mitral regurgitation (MR) has been shown to have diagnostic and prognostic benefits.(3) Impairment of left ventricular (LV) contractile reserve and development of right ventricular (RV) dysfunction on exercise are associated with adverse outcomes and identify patients, who represent a high-risk subset and may potentially benefit from an early surgical referral.(81, 125) While EX-TTE is widely available, it is bound by several limitations, similar to resting TTE.(77) As CMR is the reference-standard for LV and RV volume and function assessment(14, 15), and MR quantification by CMR has prognostic associations(56, 57), exercise-cardiovascular magnetic resonance imaging (EX-CMR) can be potentially very helpful in assessment of patients with valve disease, particularly asymptomatic patients with primary MR. Not only has EX-CMR been shown to be feasible and reproducible in healthy volunteers(82), we have also demonstrated its feasibility and reproducibility in patients with MR (Chapter 3).

As both techniques have their own advantages and offer useful diagnostic and prognostic information, combining the two techniques holds promise for

an accurate and efficient assessment of patients with valvular heart disease, especially those with asymptomatic primary MR. **(Figure 4-1)**

Figure 4- 1 Rationale for 4DF-CMR in exercise development.



CMR=cardiovascular-magnetic resonance.

A clinically applicable 4DF-CMR pulse sequence suitable for acquisition during exercise, however, has not yet been developed. Challenges encountered during 4D-flow CMR acquisition during exercise include motion artefact, heart rate variability, low signal-to-noise ratio (SNR) and mis-triggering. By applying changes to different aspects of the 4DF sequence, we aim to develop a pulse sequence, that will allow the acquisition of 4DF-CMR during exercise of high enough SNR to be analysable and clinically applicable.

The aims of this 4DF-CMR in exercise pulse sequence development included: 1) optimising parameters of the standard, clinical 4DF-CMR pulse sequence, so that image acquisition does not abort during exercise in the

presence of elevated heart rate, 2) optimise the standard, clinical 4DF-CMR pulse sequence parameters in attempt to acquire 4DF images during exercise and test on healthy volunteers, 3) once/if a promising pulse sequence has been developed, to test its feasibility in healthy volunteers.

4.3 Methods

4.3.1 Study population

This was a prospective, single-centre pulse sequence development and feasibility study. The development of the pulse sequence was carried out under the guidance of MB (4DF expert) and DH (CMR physicist). The study was approved by the National Research Ethics Service (18/YH/0168), had institutional approval and complied with the Declaration of Helsinki. All patients provided written informed consent.

4.3.2 Exercise protocol

Patients exercised on a supine cycle ergometer (Lode BV, Netherlands) during the CMR scan. Exercise protocol used in this study was in accordance with the heart rate reserve (HRR) and an age predictive maximal heart rate model(13). In line with this model, an individual low (30-39% HRR) and moderate (40-59% HRR) exercise intensity was defined for each patient. The age-predictive maximal heart rate was calculated as per the following formula(13):

age-predictive maximal heart rate = 208 - 0.7 x age.

The low and moderate intensities were calculated as per the Karvonen method.(114) This method was used as it takes into account the lower resting and exercise heart rate, which occurs in supine position. Following resting imaging, patients exercised with no resistance (0 Watts) for 1 minute, with a subsequent increase in the resistance by 25 Watts every 2 minutes and ideally 60-70 revolutions per minute. This was continued until the moderate intensity target heart rate was reached and stabilised for at least 30s, at which point CMR scanning was performed. When required, small increase in resistance were carried out to maintain the target heart rate. Patients exercised continuously with the CMR scanning undertaken during exercise, with navigated free-breathing pulse sequence and with the receiver coil strapped to the patient to reduce motion artefact.

4.3.3 CMR protocol

The CMR scan protocol (1.5T Philips Ingenia, Best, Netherlands) used in this study was previously validated in healthy volunteers in our centre(9).

CMR scan protocol (Figure 1) included:

a) Survey images

b) Free-breathing transverse Half-Fourier Acquisition Single-shot Turbo spin Echo imaging

c) Cine images acquired with breath-hold balanced steady-state free precession sequence:

a. 4-chamber view and vertical-long axis view
b. 2 orthogonal left ventricular outflow tract views

c. Left ventricular short-axis stack. Sequence parameters: typical field-of-view 360mm, 10mm slice thickness with 0mm gap, repetition time 3.2ms, echo time 1.58ms, flip angle 60°, sensitivity encoding factor 2, 30 reconstructed phases, acquired matrix 192x132 and acquired voxel size 1.88x1.88mm.

d) Through-plane aortic phase contrast images (PCMR): planned at sino-tubular junction and orthogonal to the vessel.(14) Velocity encoding was set to 150cm/s. Sequence parameters: typical field-of-view 350x282mm, slice thickness 8mm, repetition time 4.9ms, echo time 2.9ms, flip angle 15°, number of signal averages 1, sensitivity encoding factor 2, 30 reconstructed phases, acquired matrix 140x113, acquired voxel size 2.5x2.5mm, Cartesian sampling, turbo field echo factor 3.

e) Compressed-SENSE (C-SENSE) protocol:

a. C-SENSE 3 left ventricular short-axis stack: free-breathing, respiratory navigated continuous imaging with C-SENSE acceleration - factor of 3. Imaging parameters: typical field-of-view 300x300mm, repetition time 2.4ms, echo time 1.2, flip angle 60°. Multishot turbo field echo factor 12, acquired heart phases 34, slice thickness 10mm, 0mm gap, acquired voxel size 2.5x3.45mm, acquired matrix 120x87.

b. C-SENSE 3 through-plane aortic phase contrast imaging stack: free-breathing, respiratory navigated continuous imaging with C-SENSE acceleration - factor of 3. Three 8mm overlapping slices were acquired with a -3mm gap to account for increased motion during exercise, so that the centres of the individual slices were 5mm apart. Imaging parameters: typical field-of-view 350x320mm, repetition time

4.9ms, echo time 2.9ms, flip angle 15°, number of signal averages 1, turbo field echo factor 5, slice thickness 8mm, 30 reconstructed phases, acquired voxel size 2.5×2.5mm, acquired matrix 140x112, Cartesian sampling.

f) 4DF-CMR Turbo Field Echo with C-SENSE factor of 9 (final pulse sequence): typical field-of-view 300x350mm, voxel size 3x3x3mm, C-SENSE factor of 9, temporal resolution 40ms, acquired matrix 120x140, R-R window 100%, strong denoising, non-linear stretching, VENC 150cm/s.

Moderate-intensity exercise (Mod-EX) imaging

a) Free-breathing 4-chamber view and a left ventricular outflow tract view to allow re-planning of the short-axis cine imaging and phase-contrast imaging

b) C-SENSE 3 left ventricular short-axis stack: as per rest imaging

c) C-SENSE 3 through-plane aortic phase contrast imaging stack: as per rest imaging, except for velocity encoding, which was increased to 250cm/s

d) 4DF-CMR Turbo Field Echo with C-SENSE factor of 9: typical field-of-view 300x350mm, voxel size 3x3x3mm, C-SENSE factor of 9, temporal resolution 40ms, acquired matrix 120x140, R-R window 100%, strong denoising, non-linear stretching, VENC 300cm/s.

4.3.4 CMR image analysis

Analysis was performed by MG using post-processing software (cvi42, Circle Cardiovascular Imaging, Calgary, AB, Canada). Left and right ventricular volumes were obtained by manually tracing the endocardial border in end-diastole and end-systole, with trabeculations and papillary muscles being included in the blood pool. Final volumes were obtained by the summation of

discs method.(15) Aortic flow was quantified by manually tracing the endovascular border in every phase. The slice closest to the sino-tubular junction was chosen from the exercise PCMR stack for quantification of aortic flow at exercise to ensure consistency of results.

4.3.5 4DF-CMR image analysis

All 4DF-CMR data were analysed by MG (fellow). All scans were subsequently reviewed by MB (4DF expert) to provide guidance on further attempts to acquire better quality images. Images were analysed using standard Caas MR Solutions software (Pie Medical Imaging, Maastricht, The Netherlands). Aortic valve, pulmonary valve and mitral valve annulus were tracked using automated retrospective valve tracking in two orthogonal views.(20) Automated tracking was reviewed in each phase, and manually corrected as required. Flow was estimated for the aortic, pulmonary and mitral valve, if feasible. Flow contours were adjusted manually in each phase. Pulmonary valve flow was estimated to provide a means of internal validation of results of flow volumes across the three valves. Image quality was scored as: 0-very poor/non-diagnostic, 1-poor, 2-good, 3-excellent. The degree of aliasing was scored as: 0-none, (1/+)-mild, (2/++)-moderate, (3/+++)-severe.

4.3.6 Statistical analysis

Continuous variables are presented as mean±SD or median with interquartile range as per normality of distribution. Normal distribution was

determined by Anderson-Darling test. All analyses were performed using Minitab (version 19).

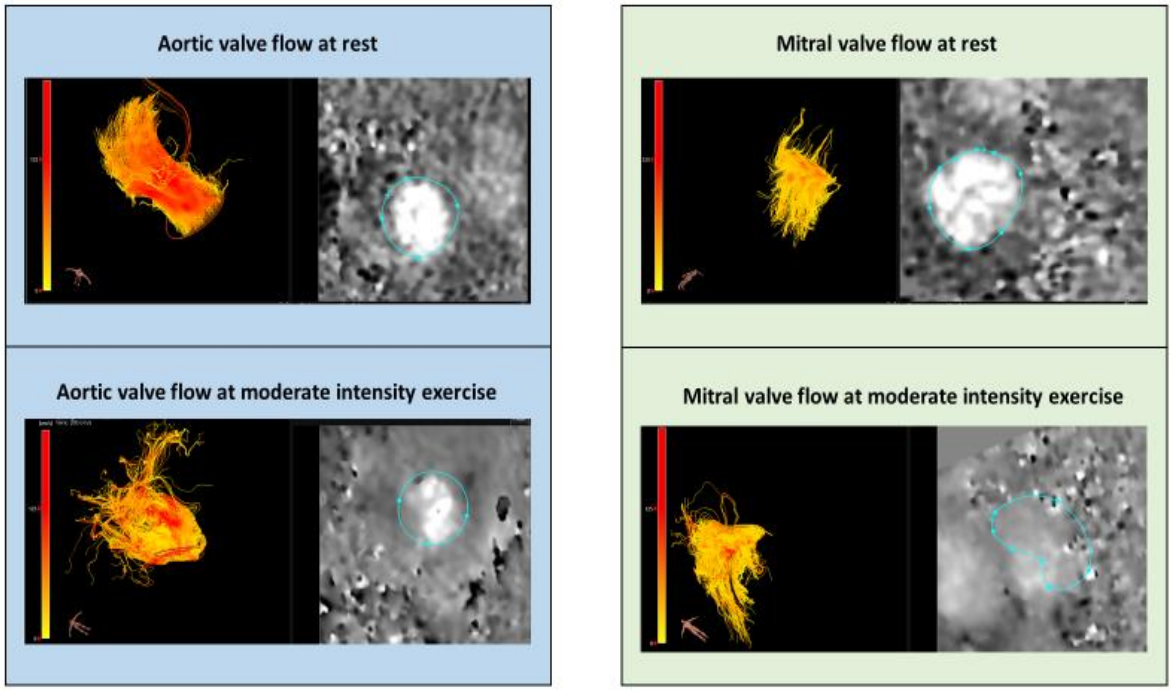
4.4 Results

4.4.1 Part 1-Pulse Sequence Development attempts

Attempt 1

Extending R-R interval to 100% prevented the scan from aborting. However, image quality was completely non-diagnostic. **(Figure 4-2)**

Figure 4- 2Example of 4DF-CMR at rest and during moderate-intensity exercise at the beginning of the 4DF-CMR in exercise pulse sequence development.



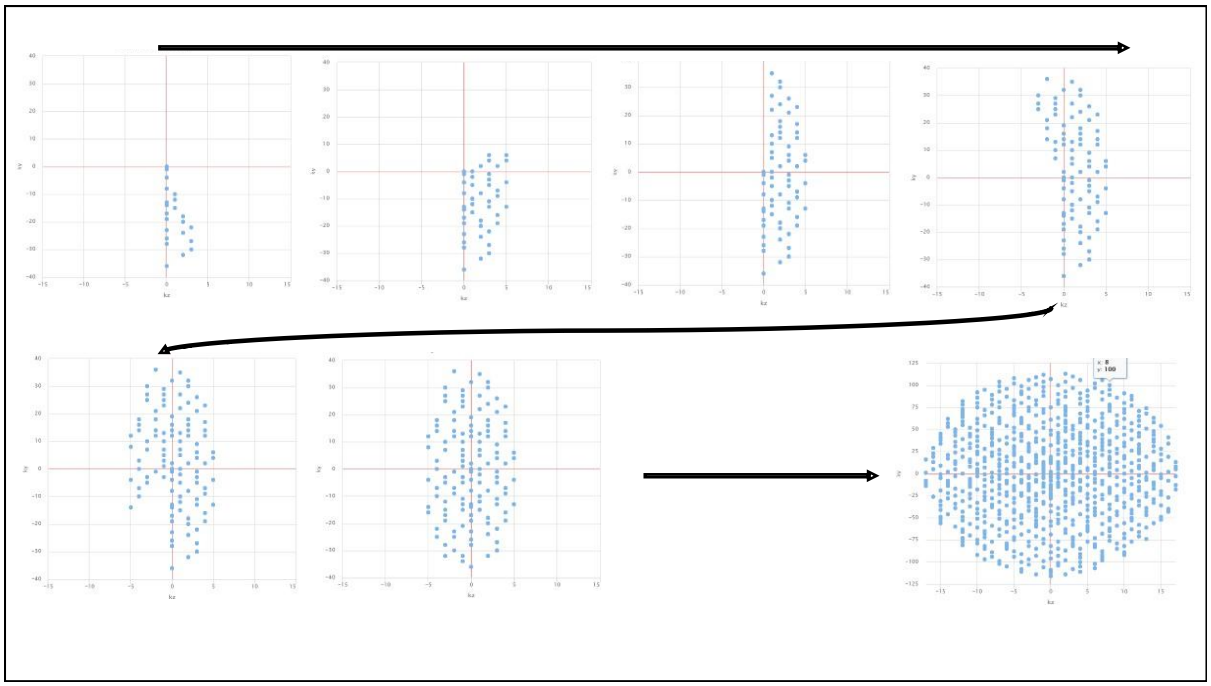
Visualisation and quantification of aortic valve and mitral valve flow by 4D-flow CMR at rest and during moderate intensity exercise.

Attempt 2

Applying 'radial CENTRA' k-space order **(Figure 4-3)** allowed the acquisition of data with heart rate at moderate-intensity level, despite stopping exercise

30 seconds into the acquisition. As ‘radial CENTRA’ k-space order enables filling in of the central portion of k-space first (flow data), exercise can be stopped at the beginning of acquisition, thus reducing motion artefact, but yet obtaining 4DF data at a heart rate in the moderate-intensity zone. We utilised C-SENSE (CS) factor of 8 for this attempt, as suggested by the physicist, who found in his prior work, that CS8 and CS9 tended to produce most consistent results.

Figure 4- 3 Visual representation of ‘radial CENTRA’ k-space order acquisition.



In ‘radial CENTRA’ k-space order aquisition (non-Cartesian k-space order), the low spatial frequency data including the flow data is acquired first, whereas the high spatial frequency data is acquired last. The order of acquisition follows a spiral trajectory from the centre of the k-space outward.

Attempt 3

We continued to use ‘radial CENTRA’ k-space order, however in this attempt we utilised C-SENSE factor of 9 to reduce the acquisition time and to improve accuracy of flow data, as previous experience suggested that CS8 underestimated flow. As per calculation of DH, it takes 16% of the entire acquisition time to complete the first cycle of data (flow data) if using the ‘radial CENTRA’ k-space order, thus the exercise in this attempt was discontinued after 16% of the estimated time of the entire acquisition.

Attempt 4

Continued use of CS9. In this attempt, we tried to reduce exercise to 10% of the acquisition time to reduce the motion artefact. This however reduced image quality. We have also tried different temporal and spatial resolution: temporal resolution of 40ms and isotropic voxel of 3mm vs. temporal resolution of 20ms and isotropic voxel off 2.5mm. The former resulted in better quality images by visual assessment.

Attempt 5

In this attempt we used temporal resolution of 40ms and isotropic voxel size of 3mm. We also increased VENC to 300cm/s in view of aliasing found in previous attempts. Exercise was stopped at 16% of the total estimated acquisition time. We also applied strong denoising and non-linear stretching. We acquired 2 sets of 4DF data with this attempt, at different level of resistance: low vs. high. Higher level of resistance resulted in more upper body stability and less motion artefact.

Attempt 6

In this attempt we added planning images just before the acquisition of 4DF data, to allow more accurate valve tracking. These included a 4-chamber

view, 2-chamber view and 2 orthogonal LVOT views. In this attempt, we were able to obtain reasonable quality images of the mitral valve flow, but poor-quality images of the aortic valve flow. We hypothesised this was due to excessive aortic motion during each cardiac cycle in very young, healthy volunteers. We therefore planned to evaluate this pulse sequence in older individuals.

4.4.2 Part 2-Validation of the above pulse sequence in healthy volunteers 37 years-of-age or above

Demographic characteristics

There were 10 healthy volunteers, who participated in the validation part of the study. Mean age was 45±7 years ; male n=8(80%). All volunteers completed the entire CMR protocol without complications. Reconstruction of 4DF data was possible in 9 out of 10 cases, whereas the data was corrupt in one case, thus no 4DF images were available for review in that.

Image quality

Image quality of the mitral valve flow, aortic valve flow and pulmonary flow in all the volunteers is presented in **Table 4-1**. Other than one volunteer, who had excellent quality images for these 3 valves, all other 4DF acquisitions were severely affected by motion artefact.

Table 4- 1 4DF-CMR in exercise image quality in all the volunteers.

Volunteer number	**Mitral flow**	**Aortic flow**	**Pulmonary flow**
1	1	1	2

2	3	3	3
3	0	0	0
4	Corrupt reconstruction	Corrupt reconstruction	Corrupt reconstruction
5	0	1	1
6	1	0	2
7	2	0	2
8	1	0	1
9	0	0	2
10	1	1	2
Mean±SD/ Median(IQR)	1±1	0(0-1)	2(1-2)

Image quality as per visual assessment: 0-very poor/non-diagnostic, 1-poor, 2-good, 3-excellent. IQR=interquartile range; SD=standard deviation.

The degree of aliasing

The degree of aliasing for each valve in all the volunteers is presented in **Table 4-2**. Pulmonary valve flow was least affected by aliasing, whereas aortic and mitral valve flow images were severely degraded by aliasing.

Table 4- 2 The degree of aliasing in mitral, aortic and pulmonary flow in all the volunteers.

Volunteer number	**Mitral flow**	**Aortic flow**	**Pulmonary flow**
1	++	+++	-
2	-	-	-
3	+++	+++	+++
4	Corrupt reconstruction	Corrupt reconstruction	Corrupt reconstruction
5	++	-	-
6	+	+++	-
7	-	+++	-
8	+++	+++	-
9	+	+++	-
10	-	+	-
Mean±SD/ Median(IQR)	1.3±1.3	3(1.5-3)	0(0-0)

The degree of aliasing was scored as: 0-none, (1/+)-mild, (2/++)-moderate, (3/+++)-severe. IQR=interquartile range; SD=standard deviation.

Quantification of flow in volunteer number 2

As volunteer number 2 was the only case with excellent quality images and no aliasing, quantification of flow by 4DF-CMR and PCMR was performed.

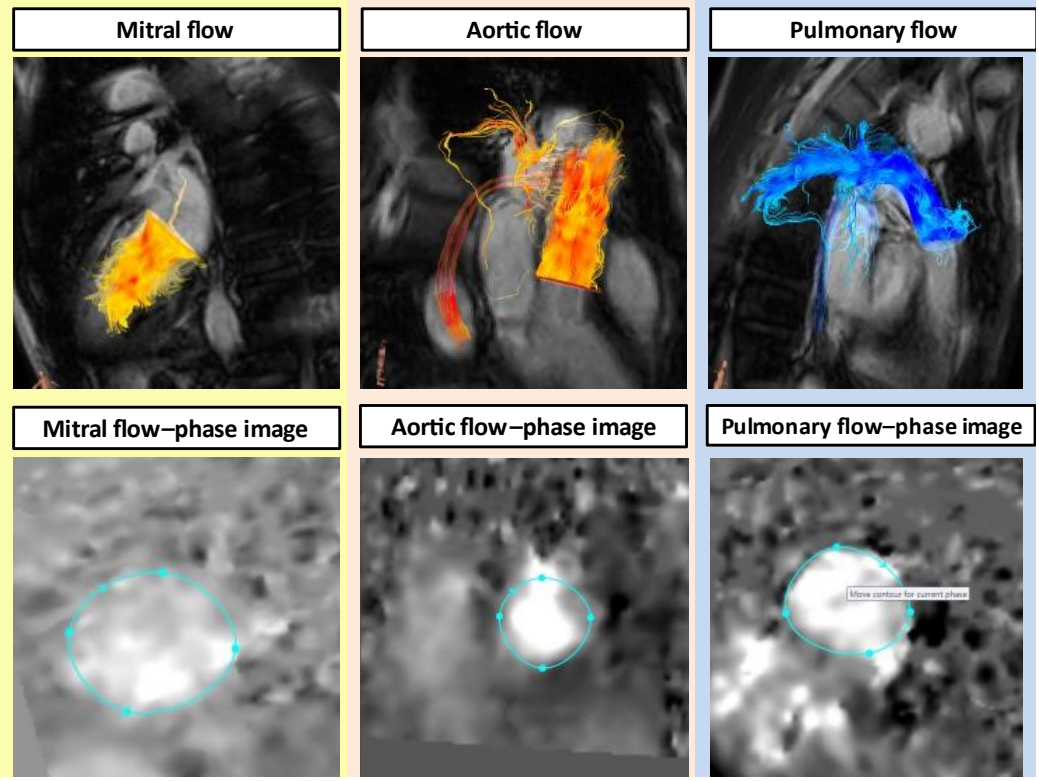
The results are presented in **Table 4-3.** The quality of images in this volunteer is presented in **Figure 4-4.**

Table 4- 3 Quantification of valvular flow and LV volumes by 4DF-CMR and PCMR in volunteer 2.

4DF-CMR	**MV forward flow**	**MV backward flow**	**MV effective flow**	**AV forward flow**	**AV backward flow**	**AV effective flow**	**PV forward flow**	**PV backward flow**	**PV effective flow**
Rest	95ml	6ml	89ml	86ml	2ml	84ml	76ml	7ml	69ml
Exercise	131ml	5ml	126ml	105ml	1ml	104ml	145ml	1ml	144mls
PCMR	**LV end-diastolic volume**	**LV end-systolic volume**	**LV stroke volume**	**AV forward flow**	**AV backward flow**	**AV effective flow**	**PV forward flow**	**PV backward flow**	**PV effective flow**
Rest	176ml	77ml	99ml	86ml	2ml	84ml	95ml	1ml	94ml
Exercise	195ml	76ml	119ml	98ml	1ml	97ml	94ml	2ml	92ml

AV=aortic valve; LV=left ventricle; MV=mitral valve; PV=pulmonary valve.

Figure 4- 4 Image quality of 4DF-CMR during exercise in volunteer 2.



4.5 Discussion

During pulse sequence development part of this study, we were able to optimise a standard, clinical 4DF-CMR pulse sequence, so that it did not abort during exercise in the presence of elevated heart rate. Further optimisation of the pulse sequence resulted in 4DF images of mitral valve flow being potentially diagnostic. We subsequently attempted to validate this pulse sequence, however, other than one volunteer, who had excellent quality images with no aliasing, all other 4DF datasets were severely affected by motion artefact and aliasing.

4.5.1 Four-dimensional flow CMR in exercise

To our knowledge, there is only one study, which evaluated 4DF-CMR during exercise.(133) This study, however, evaluated aortic and pulmonary vessel flow and kinetic energy, rather than valvular flow. While kinetic energy assessment was suboptimal, the vessel flow was quantifiable and reproducible.(133) There are, however, no successful studies of valvular flow assessment by 4DF-CMR during exercise. Prior studies have shown, that PCMR assessment of valvular flow and LV volumes is feasible and reproducible not only in healthy volunteers(79, 82), but we have also shown it is feasible and reproducible in patients with primary MR (Chapter 3). Likewise, 4DF-CMR assessment of valvular flow at rest is highly reproducible and accurate(70). Combining these two techniques would therefore offer several potential advantages in the assessment of valvular heart disease. While our PSD was not successful, we did manage to acquire 4DF datasets during moderate-intensity exercise. Although most 4DF datasets were severely degraded by motion artefact and aliasing, with poor SNR, we did manage to acquire excellent quality images in one volunteer and good images of pulmonary valve flow. This holds promise for future developments.

4.5.2 Limitations and future directions

While we attempted to optimise several parameters to develop a clinically applicable pulse sequence, there are still a number of adjustments that could be attempted in the future. One of the biggest limitations was the large size of the coil, which resulted either in patients moving the coil during cycling

with their thighs or requiring extra padding in between the coil and the chest, which invariably increased the distance between the coil and the heart, severely reducing the signal-to-noise ratio. A small cardiac coil would have resolved both of these issues. It also would be much easier to securely strap the coil to the patient, if the coil was smaller. Potentially, using a different pulse sequence altogether or a different vendor, would have provided different results. Shorter acquisition time and automatic reconstruction would have potentially resulted in better quality images and successful reconstruction in all cases.

4.6 Conclusion

Developing a clinically applicable 4DF-CMR pulse sequence for use during continuous exercise would potentially have several diagnostic and prognostic advantages in the assessment of valvular heart disease. Being the first group to attempt to develop such a pulse sequence has identified many challenges, many of which were insurmountable during the limited timeframe of this thesis. Although ultimately we were unsuccessful in producing a stable pulse sequence that delivered acceptable image quality, we believe that the advancements we have made will help with future developments in this disease area.

Chapter 5
Silent cerebral infarction and clinical outcomes in surgically treated mitral valve disease

5.1 Abstract

Background: While stroke is a rare complication of cardiac surgery, perioperative silent cerebral infarction may occur more frequently. However, in terms of mitral valve surgery, there are no dedicated studies describing its incidence or clinical significance.

Objectives: Exploratory study to ascertain the incidence of silent perioperative cerebral infarction in mitral valve surgery and to examine its influence on quality of life, functional capacity and clinical outcomes.

Methods: Prospective, single-centre, observational cohort study. We included patients with primary/atrial mitral regurgitation scheduled for either mitral valve surgery or 'watchful waiting'. Patients underwent paired cerebral diffusion-weighted MRI scans pre- and post-operatively, or at baseline and 6-months if 'watchful waiting', as well as quality of life questionnaires (EuroQoL 5-dimensions, 36-Item Short Form Health Survey) and functional assessments (6-minute walk test; 6MWT). Major Adverse Cardiovascular Events (MACE) were recorded, including all-cause death, myocardial infarction, stroke/transient ischaemic attack, hospitalisation for heart failure and an acute hospitalisation for an arrhythmia.

Results: Seventy-seven patients performed paired cerebral MRI scans (mitral valve repair (MVr) n=29, mitral valve replacement (MVR) n=21,

'watchful waiting' group n=27). Demographic and clinical characteristics were comparable between groups. Only 1 (3.7%) patient in the 'watchful waiting' group had new silent cerebral infarction. Overall incidence of perioperative silent cerebral infarction was 36%; there were proportional but not significant differences in the incidence between MVr and MVR (n=7(24.1%) vs. n=11(52.3%), respectively; p=0.07). There were no significant differences between the cerebral infarct characteristics in MVr and MVR patients, other than median volume per infarct, which was larger in the MVR group (MVr=0.10ml (IQR 0.05-0.13) vs. MVR=0.22ml (0.13-0.49); p=0.02). There was no significant difference in the 6-month change in quality of life measures or the functional capacity between those with a new silent cerebral infarct and those without. In the surgical groups, MACE event rates at 40 months (IQR 12-54) were no different in patients with a new cerebral infarction and those without (p=0.61).

Conclusions: Mitral valve replacement compared to repair had proportionally but not significantly greater incidence of perioperative silent cerebral infarction and larger lesion volume. However, these silent cerebral infarcts appeared to have no negative impact on general quality of life, functional capacity or MACE rates.

5.2 Introduction

Mitral regurgitation (MR) is the second most common valvular pathology worldwide, with community prevalence of severe MR of more than 1%.(83, 134) When untreated, severe mitral regurgitation is associated with significant morbidity and mortality.(50) Therefore, current guidelines

recommend surgical intervention in patients with symptoms and those with evidence of adverse left atrial or left ventricular remodelling.(1, 3)

Stroke is a recognised complication of mitral valve surgery and is frequently associated with devastating consequences including post-operative mortality and disability.(84) Although silent cerebral infarction has been shown to occur considerably more frequently than overt stroke in patients undergoing cardiac surgery, there is no consensus as to its clinical significance.(85-88, 92) Furthermore, there are no studies focused on incidence or characteristics of silent cerebral infarction in mitral valve surgery. Prior studies utilized diffusion-weighted magnetic resonance imaging (DWI-MRI) to detect perioperative cerebral embolic infarction in patients undergoing coronary artery bypass grafting(88, 96) and transcatheter aortic valve replacement(90, 95), with a small number of studies including open valve surgery.(87, 92, 135) The perioperative incidence of silent cerebral embolic infarction varied widely between these studies, as did the impact on neurocognitive function and quality of life.(92)

There are no data with regard to the incidence of silent perioperative cerebral infarction following mitral valve surgery. Whether the incidence differs between mitral valve repair and mitral valve replacement, and whether these embolic events have any influence on medium-term health-related quality of life is presently unknown. Therefore, we sought to ascertain the incidence of perioperative silent cerebral infarction in patients undergoing mitral valve repair and replacement and to determine its impact on medium-term health-related quality of life, functional capacity and clinical outcomes.

5.3 Methods

5.3.1 Study design and population

This was a prospective, single-centre, observational cohort study, which recruited patients with at least moderate mitral regurgitation, who were either awaiting mitral valve surgery (repair or replacement) or who were undergoing ‘watchful waiting’.

The grading of at least moderate mitral regurgitation was confirmed by the multi-disciplinary heart team based on transthoracic and/or transoesophageal echocardiography according to ASE criteria.(100) In accordance with European Society of Cardiology guidelines(1), patients with primary mitral regurgitation were referred for mitral valve surgery if they were either symptomatic or exhibited predictors of adverse outcomes, such as impaired left ventricular ejection fraction ≤60%, left ventricular end-systolic diameter ≥45mm, new-onset atrial fibrillation or elevated pulmonary pressures >50mmHg. In patients with atrial mitral regurgitation, surgery was recommended primarily in those who were symptomatic despite appropriate medical therapy. Surgical referral, timing and procedural selection was based on clinical factors, and made by the multi-disciplinary heart team and the patient, through a process of shared decision making. Patients who were asymptomatic and did not meet surgical criteria underwent ‘watchful waiting’ with serial echocardiograms and clinical assessments in a dedicated Valve Clinic. Acute silent cerebral infarction was defined as the presence of new restricted diffusion lesions on DWI in the absence of a focal neurological deficit.(92)

Exclusion criteria included mitral regurgitation of ischaemic or rheumatic aetiology and general contraindications to MRI. The study was approved by the National Research Ethics Service (15/YH/0503), had institutional approval and complied with the Declaration of Helsinki. All patients provided written informed consent.

5.3.2 Mitral valve surgery

Mitral valve surgery was performed according to standard surgical practice, including midline sternotomy, cardiopulmonary bypass technique, systemic heparinisation and mild systemic hypothermia. The procedure was guided by intra-operative transoesophageal echocardiography. Mitral valve repair was performed using Gore-Tex chordae sutures and a Carpentier-Edwards annuloplasty ring, whereas mitral valve replacement was performed using Edwards Perimount Magna bioprosthetic valve, St. Jude Epic™ Mitral stented tissue valve with Linx™ AC technology or St. Jude mechanical valves. Other interventions, such as tricuspid valve repair, coronary artery bypass grafting and surgical left atrial ablation were performed if clinically indicated. Lifelong anticoagulation with a vitamin K antagonist was prescribed for all mechanical prostheses. In the absence of secondary indication for anticoagulation, patients with a bioprosthetic valve and mitral valve repair discontinued their anticoagulation after 3 months.

5.3.3 Study assessments

Cerebral MRI

Patients underwent paired identical cerebral MRI scans (1.5T Phillips Ingenia, Best, Netherlands) using a dedicated head coil. The first scan was performed immediately prior to surgery or at the time of baseline

assessment for patients undergoing ‘watchful waiting’. Post-procedural cerebral MRI was performed pre-discharge for surgical patients and at 6-month follow-up for patients managed by ‘watchful waiting’.

Cerebral MRI protocol:

a) Survey images
b) T2-weighted fast field echo (slice thickness 5mm, 29 slices, gap 0.75mm, echo time 26ms, flip angle 20°, field-of-view 240mm)
c) T2-weighted turbo spin echo (slice thickness 5mm, 29 slices, gap 0.75mm, echo time 93ms, flip angle 90°, field-of-view 230mm)
d) Diffusion-weighted imaging (slice thickness 5mm, 29 slices, gap 0.75mm, echo time - shortest, flip angle 90°, field-of-view 240mm)

Cerebral MRI image analysis

Analysis was performed by 2 experienced neuroradiologists (HM and AJPG) blinded to all clinical and procedural details, using standard post-processing software (cvi42, Circle Cardiovascular Imaging, Calgary, AB, Canada). New restricted diffusion lesions on DWI defined acute cerebral infarction. Location, vascular territory, number of lesions, size of the largest lesion (<5mm or >5mm) and total lesion volume (ml) were recorded.

Health-Related Quality of Life assessment

Quality of life and performance of activities of daily living were assessed by validated patient-reported health status questionnaire: EuroQoL 5-dimensions (EQ-5D-5L). These were administered at baseline assessment and at 6-months follow-up. The EQ-5D-5L questionnaire consists of a descriptive section and a visual analogue scale. The descriptive section assessed health state in 5 domains and at 5 severity levels: mobility, self-

care, usual activities, pain/discomfort and anxiety/depression; these were rated by patients in the order of increasing severity from ‘no problems’(=1) in a particular domain to ‘extreme problems/unable to perform’(=5). A single index value was derived to summarise the health states for each patient (based on a US value set) and to facilitate comparison of outcomes between the groups(136, 137). The visual analogue scale allowed patients to rate their health on a scale of 1-100, with 100 being ‘the best health you can imagine’.

Six-minute walk test

Functional exercise capacity was assessed at baseline and at the 6-month follow-up utilising the 6-minute walk test (6MWT) distance (m), which was performed in accordance with the American Thoracic Society guidelines.(105)

Clinical Outcomes

Major Adverse Cardiovascular Events (MACE) were defined as the composite of all-cause death, myocardial infarction, stroke/transient ischaemic attack, hospitalisation for heart failure and acute hospitalisation for arrhythmia.

5.3.4 Statistical analysis

Continuous variables are presented as mean±SD or median with interquartile range as per normality of distribution. Normal distribution was determined by Anderson-Darling test. Categorical variables are expressed as numbers and percentages. Continuous variables were compared by means of Student *t*-test (normal distribution) or Mann-Whitney test (non-normal distribution). Categorical variables were compared using Fisher’s

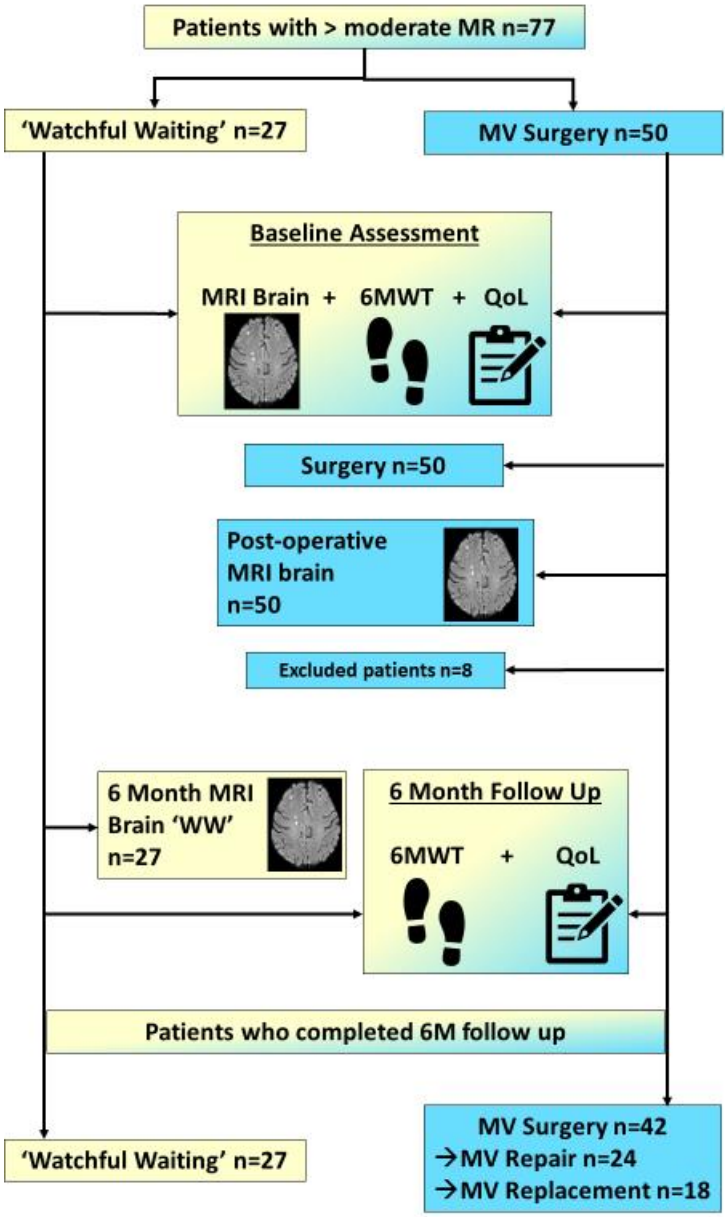
Exact test. Multiple linear regression analysis was performed to evaluate the relationship between patient and operative factors and the number of new cerebral infarcts. Variables with a $P<0.1$ were subsequently entered into mixed selection stepwise regression analysis. All analyses were performed using Minitab (version 19) and statistical significance was defined as $P<0.05$.

5.4 Results

5.4.1 Demographic, clinical characteristics and surgical procedural data

Of the 77 patients enrolled with paired cerebral MRI, 27 were in the 'watchful waiting' group and 50 in the mitral valve surgery group (**Figure 5-1).**

Figure 5- 1 Study assessments.



MR=mitral regurgitation; MRI=magnetic-resonance imaging; MV=mitral valve; QoL=quality of life assessment; 'WW'='watchful waiting'; 6MWT=6-minute walk test.

'Watchful Waiting' vs. MV Surgery

There were no major demographic or clinical differences between the watchful waiting and surgical groups **(Table 5-1)**; in particular, there were no significant differences in the body mass index status, EuroSCORE II or the

co-morbidities between these groups. Patients in the ‘watchful waiting’ group were less symptomatic, with 17(63%) patients having New York Heart Association class 1 dyspnoea vs. 9(18%) patients in the surgical group; $p<0.001$. In both groups, the majority of patients had MR secondary to posterior mitral valve prolapse (‘watchful waiting’ group n=14(51.9%) and MV surgery group n=36(72%); p=0.09).

Table 5- 1 Baseline patient characteristics in 'Watchful Waiting' vs. Mitral Valve Surgery group.

Variable	**Watchful Waiting n=27**	**MV Surgery n=50**	**p-value**
Age (years)	71(59-80)	70(64-74)	0.58
Male, n(%)	16(59.3)	40(80)	0.06
BMI (kg/m^2)	24.5±4.1	26.1±5	0.13
EuroSCORE II	1.07(0.62-2.45)	1.27(0.86-2.92)	0.24
NYHA Class I, n(%)	17(63)	9(18)	**<0.001**
NYHA Class II, n(%)	5(18.5)	25(50)	**0.008**
NYHA Class III, n(%)	5(18.5)	16(32)	0.29
NYHA Class IV, n(%)	0(0)	0(0)	-
Hypertension, n(%)	5(18.5)	17(34)	0.19
Type 2 Diabetes Mellitus, n(%)	1(3.7)	2(4)	1
Atrial fibrillation, n(%)	11(40.7)	29(58)	0.16
Prior stroke/TIA, n(%)	2(7.4)	3(6)	1
Prior MI, n(%)	2(7.4)	1(2)	0.30
COPD, n(%)	3(11.1)	1(2)	0.12

Creatinine (μmol/L)	85(67-94)	86(76-99)	0.43
Haemoglobin (g/L)	134±13	141±14	0.03
MR Aetiology			
Posterior MVP, n(%)	14(51.9)	36(72)	0.09
Anterior MVP, n(%)	1(3.7)	6(12)	0.41
Bileaflet MVP, n(%)	7(25.9)	6(12)	0.20
Flail leaflet, n(%)	4(14.8)	16(32)	0.11
Atrial, n(%)	4(14.8)	2(4)	0.18

Data are presented as mean±SD, median(IQR1-IQR3) and n(%). BMI=body mass index; COPD=chronic obstructive pulmonary disease; EuroSCORE=European System for Cardiac Operative Risk Evaluation; MI=myocardial infarction; MR=mitral regurgitation; MVP=mitral valve prolapse; NYHA=New York Heart Association; TIA=transient ischaemic attack.

MV Repair vs. MV Replacement

There were no substantial differences in clinical characteristics between the MVr and the MVR groups, other than the prevalence of hypertension (MVr n=14(48%) vs. MVR n=3(14%); p=0.02) **(Table 5-2).** Surgical procedural data are also presented in **Table 5-2**. A small proportion of patients in both groups underwent concomitant coronary artery bypass grafting, tricuspid valve repair and/or surgical atrial fibrillation ablation. There was no significant difference in the cumulative bypass time or the cross clamp time between the MVr and the MVR groups. There were 5(23.8%) patients in the MVR group, in whom repair was initially attempted.

Table 5- 2 Baseline patient characteristics and operative data in Mitral Valve Repair vs. Mitral Valve Replacement group.

Variable	**MV Repair n=29**	**MV Replacement n=21**	**p-value**
Age (years)	70(63-73)	70(65-78)	0.34
Male, n(%)	25(86.2)	15(71)	0.29
BMI (kg/m^2)	26(24-29)	25(21-28)	0.30
EuroSCORE II	1.31(0.81-2.79)	1.06(0.92-3.23)	0.75
NYHA Class I, n(%)	6(20.7)	3(14)	0.72
NYHA Class II, n(%)	14(48.3)	11(52)	1
NYHA Class III, n(%)	9(31)	7(33)	1
NYHA Class IV, n(%)	0(0)	0(0)	-
Hypertension, n(%)	14(48.3)	3(14)	**0.02**
Type 2 Diabetes Mellitus, n(%)	0(0)	2(10)	0.17
Atrial fibrillation, n(%)	18(62.1)	11(52)	0.57
Prior stroke/TIA, n(%)	1(3.4)	2(10)	0.57
Prior MI, n(%)	1(3.4)	0(0)	1
COPD, n(%)	0(0)	1(2)	0.42

Creatinine (µmol/L)	86±18	89±22	0.62
Haemoglobin (g/L)	141±16	142±11	0.64
MR Aetiology			
Posterior MVP, n(%)	24(82.8)	12(57)	0.06
Anterior MVP, n(%)	1(3.4)	5(24)	0.07
Bileaflet MVP, n(%)	2(6.9)	4(19)	0.22
Flail leaflet, n(%)	10(34.5)	6(29)	0.76
Atrial, n(%)	2(6.9)	0(0)	0.50
Operative data			
Concomitant CABG, n(%)	1(3.4)	3(14.3)	0.30
Concomitant TV repair, n(%)	5(17.2)	0(0)	0.07
Concomitant surgical AF ablation, n(%)	2(7)	1(4.8)	1
Concomitant aorta surgery, n(%)	0(0)	1(4.8)	0.42
Cumulative bypass time (min)	122(104-134)	117(95-189)	0.95
Cumulative cross clamp time (min)	87(79-106)	76(63-105)	0.14
Attempted repair, n(%)	-	5(23.8)	-

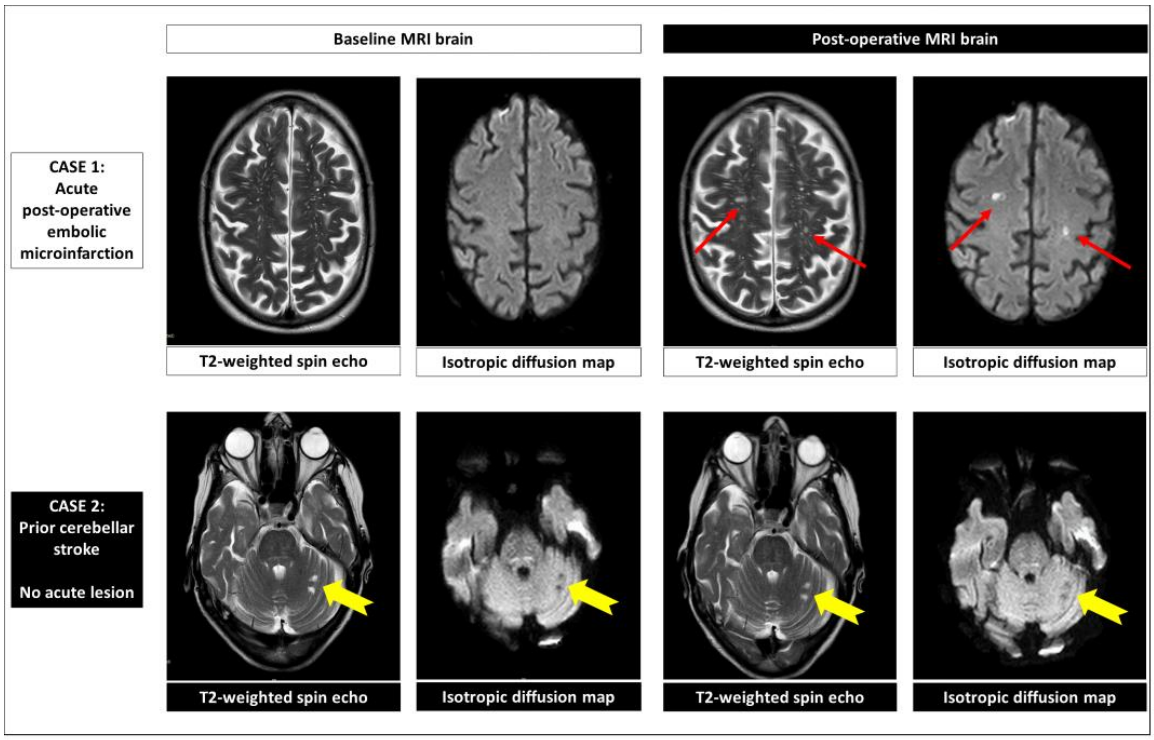
Mechanical valve, n(%)	-	9(42.9)	-

Data are presented as mean±SD, median(IQR1-IQR3) and n(%). AF=atrial fibrillation; BMI=body mass index; CABG=coronary artery bypass graft; COPD=chronic obstructive pulmonary disease; EuroSCORE=European System for Cardiac Operative Risk Evaluation; MI=myocardial infarction; MR=mitral regurgitation; MV=mitral valve; MVP=mitral valve prolapse; NYHA=New York Heart Association; TIA=transient ischaemic attack; TV= tricuspid valve.

5.4.2 Cerebral MRI

Paired cerebral MRI scans were performed in 77 patients **(Figure 5-1).** An example of the difference in the appearance between a new (perioperative) cerebral infarction and a chronic cerebral infarction on MRI is shown in **Figure 5-2.** Differences in the incidence and the characteristics of silent cerebral infarction between the three patient groups are presented in **Table 5-3**.

Figure 5- 2 An example of MRI brain images demonstrating the difference in appearance of an acute infarction vs. prior stroke.



Case 1 (top panel) demonstrates an acute post-operative infarction (red arrows), presenting as small, scattered, bilateral high intensity lesions on the post-operative T2-weighted spin echo pulse sequences and on the isotropic diffusion map. Case 2 (bottom panel) demonstrates a prior cerebellar stroke (notched yellow arrow), presenting as high intensity lesions on the T2-weighted spin echo pulse sequences, but as hypointense lesions on the isotropic diffusion map with an unchanged appearance between the baseline and the follow-up scan. MRI=magnetic-resonance imaging.

Table 5- 3 Comparison of new cerebral infarction by DWI-MRI in (A) 'Watchful Waiting' vs. MV Surgery groups, (B) following MV Repair vs. MV Replacement and (C) between DWI +ve MV Repair vs. DWI +ve MV Replacement.

(A)	**Watchful Waiting n=27**	**MV Surgery n=50**	**p-value**
Incidence of new cerebral infarction, n(%)	1(3.7)	18(36)	**0.002**
Solitary lesion, n(%)	0(0)	5(10)	0.16
Multiple lesions, n(%)	1(3.7)	13(26)	**0.02**
Right hemisphere only, n(%)	1(3.7)	3(6)	1
Left hemisphere only, n(%)	0(0)	4(8)	0.29
Bilateral infarction, n(%)	0(0)	11(22)	**0.007**
ACA territory lesion, n(%)	0(0)	7(14)	0.09
MCA territory lesion, n(%)	1(3.7)	10(20)	0.09
PCA territory lesion, n(%)	0(0)	9(18)	**0.02**

VBA territory lesion, n(%)	0(0)	7(14)	0.09
Nr of patients with small lesions <5mm, n(%)	1(3.7)	9(18)	0.09
Nr of patients with large lesions >5mm, n(%)	0(0)	9(18)	**0.02**
Volume per infarct (ml)	0.026(-)	0.15(0.10-0.39)	-
Number of new lesions per patient	0(0-0)	0(0-2)	**0.002**
Infarct volume per patient (ml)	0(0-0)	0(0-0.27)	**0.002**

Data are presented as median(IQR1-IQR3) and n(%). ACA=anterior cerebral artery; DWI-MRI=diffusion-weighted magnetic resonance imaging; MCA=middle cerebral artery; MV=mitral valve; PCA=posterior cerebral artery; VBA=vertebrobasilar artery.

(B)	**MV Repair** **n=29**	**MV Replacement** **n=21**	**p-value**
Incidence of new cerebral infarction, n(%)	7(24.1)	11(52.3)	0.07
Solitary lesion, n(%)	2(7)	3(14.3)	0.64
Multiple lesions, n(%)	5(17.2)	8(38.1)	0.12
Right hemisphere only, n(%)	1(3.4)	2(9.5)	0.57
Left hemisphere only, n(%)	3(10.3)	1(4.8)	0.63
Bilateral infarction, n(%)	3(10.3)	8(38.1)	**0.04**
ACA territory lesion, n(%)	1(3.4)	6(28.6)	**0.03**
MCA territory lesion, n(%)	4(13.8)	6(28.6)	0.29
PCA territory lesion, n(%)	2(7)	7(33.3)	**0.03**
VBA territory lesion, n(%)	3(10.3)	4(19)	0.43
Nr of patients with small lesions <5mm, n(%)	4(13.8)	5(23.8)	0.46
Nr of patients with large lesions >5mm, n(%)	3(10.3)	6(28.6)	0.14
Volume per infarct (ml)	0.10(0.05-0.13)	0.22(0.13-0.49)	**0.02**

Number of new lesions per patient	0(0-0.50)	1(0-3)	**0.046**
Infarct volume per patient (ml)	0(0-0.01)	0.05(0-0.81)	**0.02**

Data are presented as median(IQR1-IQR3) and n(%). ACA=anterior cerebral artery; DWI-MRI=diffusion-weighted magnetic resonance imaging; MCA=middle cerebral artery; MV=mitral valve; PCA=posterior cerebral artery; VBA=vertebrobasilar artery.

(C)	**DWI +ve MV Repair n=7**	**DWI +ve MV Replacement n=11**	**p-value**
Solitary lesion, n(%)	2(28.6)	3(27.3)	1
Multiple lesions, n(%)	5(71.4)	8(72.7)	1
Right hemisphere only, n(%)	1(14.3)	2(18.2)	1
Left hemisphere only, n(%)	3(42.9)	1(9.1)	0.25
Bilateral infarction, n(%)	3(42.9)	8(72.7)	0.33
ACA territory lesion, n(%)	1(14.3)	6(54.5)	0.15
MCA territory lesion, n(%)	4(57.1)	6(54.5)	1
PCA territory lesion, n(%)	2(28.6)	7(63.6)	0.33
VBA territory lesion, n(%)	3(42.9)	4(36.4)	1
Nr of patients with small lesions <5mm, n(%)	4(57.1)	5(45.5)	1
Nr of patients with large lesions >5mm, n(%)	3(42.9)	6(54.5)	1
Volume per infarct (ml)	0.10(0.05-0.13)	0.22(0.13-0.49)	**0.02**
Number of new lesions per patient	2(1-10)	3(1-6)	0.93

Infarct volume per patient (ml)	0.20(0.05-0.98)	0.66(0.33-1.48)	0.22

Data are presented as median(IQR1-IQR3) and n(%). ACA=anterior cerebral artery; DWI-MRI=diffusion-weighted magnetic resonance imaging; MCA=middle cerebral artery; MV=mitral valve; PCA=posterior cerebral artery; VBA=vertebrobasilar artery.

'Watchful Waiting' vs. MV Surgery

There was a statistically significant difference in the incidence of silent cerebral infarction between the 'watchful waiting' group and the patients who underwent MV surgery (n=1(3.7%) vs. n=18(36%)), respectively; p=0.002). The one patient in the 'watchful waiting' group who had silent cerebral infarction detected on the 6-month follow-up cerebral MRI, had small, low volume lesions, confined to the right hemisphere. The cerebral infarcts found in the surgical patients were predominantly multiple (n=13(26%)), bilateral (n=11(22%)) and larger volume (n=9(18%)) **(Table 5-3A).**

MV Repair vs. MV Replacement

There was no statistically significant difference in the incidence of cerebral infarction between the MVr and the MVR groups, although the incidence was proportionally higher in patients who underwent MVR (n=7(24.1%) vs. n=11(52.3%), respectively; p=0.07) **(Table 5-3B).** There was no group difference in the proportion of patients, who had solitary or multiple lesions, however the incidence of bilateral infarction was higher in the MVR group (MVr n=3(10.3%) vs. MVR n=8(38.1%); p=0.04). Additionally, there was a higher incidence of anterior and posterior cerebral artery territory lesions in the MVR group (p=0.03 for both).

DWI-positive MV Repair vs. DWI-positive MV Replacement

Characteristics of silent cerebral infarction were compared between the MVr and MVR patient groups. There was no significant difference between the incidence of multiple lesions, bilateral lesions or the arterial distribution of the lesions between these 2 groups. The median volume per infarct, however, was higher in the patients who underwent MVR (DWI+ve MVr 0.10ml (IQR 0.05-0.13) vs. DWI+ve MVR 0.22ml (0.13-0.49); p=0.02). There was no significant difference between the median number of new lesions per patient (DWI+ve MVr 2 (IQR 1-10) lesions vs. DWI+ve MVR 3 (1-6) lesions, p=0.93) or the median infarct volume per patient (DWI+ve MVr 0.20ml (0.05-0.98) vs. DWI+ve MVR 0.66ml (0.33-1.48); p-value 0.22) **(Table 5-3C).**

5.4.3 Functional capacity and health-related quality of life

Follow-up functional capacity and quality of life assessments were completed by all patients in the 'watchful waiting' group and 42 (84%) patients in the MV surgery group **(Figure 5-1).** The EQ-5D-5L index scores, the visual analogue scale scores and the 6MWT distance at baseline and at the 6-month follow-up in all groups are presented in **Table 5-4**.

Table 5- 4 Functional and quality-of-life assessment at baseline and at 6-month follow-up.

	US Norms*†	Baseline	6-Months	p-value
Watchful waiting n=27				
EQ-5D-5L index*	0.824±0.217	0.93(0.72-1.00)	0.87(0.57-0.94)	0.24
VAS*	80.7±15.1	80(65-90)	80(60-85)	0.58
6MWD†	631±93	369±134	367±134	0.80
MV surgery n=42				
EQ-5D-5L index	0.824±0.217	0.78(0.58-0.88)	0.87(0.78-0.96)	**0.005**
VAS	80.7±15.1	70(45-80)	80(70-90)	**0.001**
6MWD	631±93	365±89	420±83	**0.000**
MV repair n=24				
EQ-5D-5L index	0.824±0.217	0.70±0.24	0.85±0.14	**0.006**
VAS	80.7±15.1	59±22	80±11	**0.000**
6MWD	631±93	365±98	420±72	**0.006**
MR replacement n=18				

EQ-5D-5L index	0.824±0.217	0.80(0.53-0.91)	0.88(0.81-0.96)	0.09
VAS	80.7±15.1	78(45-81)	80(68-86)	0.28
6MWD	631±93	365±78	419±99	**0.007**

Data are presented as mean±SD, median(IQR1-IQR3) and n(%). EQ-5D-5L=EuroQoL 5-dimensions questionnaire; MV=mitral valve; VAS=visual analogue scale; 6MWD=six-minute walking distance. *EQ-5D-5L index and VAS score norms are reported according to US elderly population (65-74 years).(138) #6MWD norms as per 6MWD in healthy elderly subjects (50-85 years).(139)

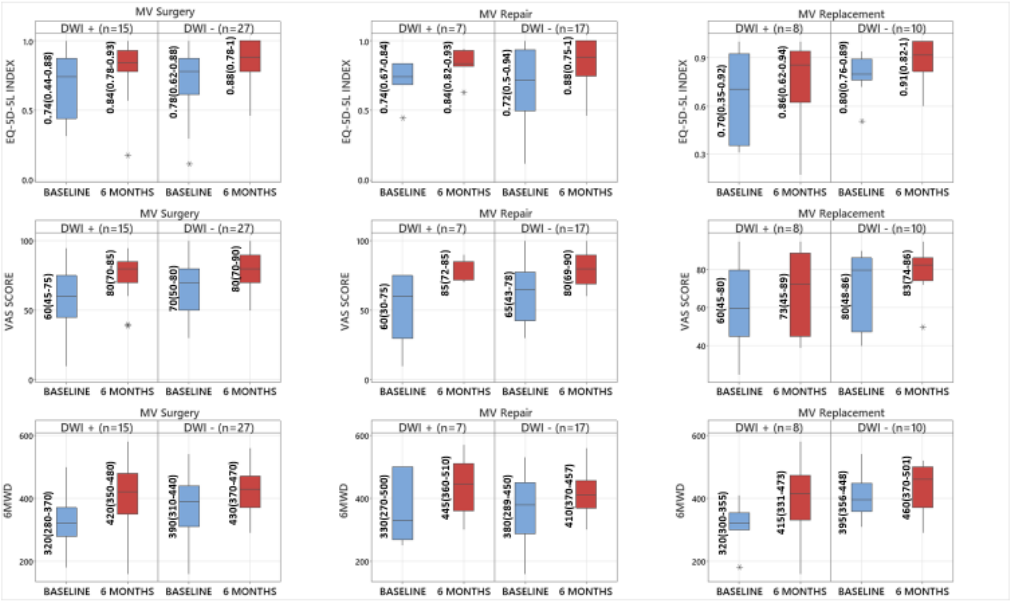
In the 'watchful waiting' group, there were no changes in the EQ-5D-5L index score, visual analogue scale score or the 6MWT distance during the 6-month follow-up. Patients who underwent MV surgery, however, had a significant improvement in the EQ-5D-5L index score (baseline 0.78(0.58-0.88) vs. 6-month follow-up 0.87(0.78-0.96); p=0.005), the visual analogue scale score (baseline 70(45-80) vs. 6-month follow-up 80 (70-90); p=0.001) and in the 6MWT distance (baseline 365±89m vs. 6-month follow-up 420±83m; p<0.001). Considering the surgical subgroup who underwent MVr, similar improvements were seen overall, however, in the MVR subgroup, the only significant change was their improvement in the 6MWT distance (baseline 365±78m vs. 6-month follow-up 419±99m; p=0.007).

5.4.4 Impact of perioperative silent cerebral infarction on quality of life and functional capacity

The surgical patients who had completed the 6-month follow-up were divided into groups based on the post-operative cerebral DWI-MRI status (positive vs. negative). The baseline and the 6-month quality of life measures and the

6MWT distance in these groups are presented in **Figure 5-3**. The change in quality of life and the 6MWT distance was compared between the patients who had new cerebral infarction (as per DWI-MRI) and those who did not **(Table 5-5).** In all groups (MV surgery, MVr and MVR), there was no statistically significant difference in the change in the EQ-5D-5L index score, the visual analogue scale score or the 6MWT distance between the patients with a new post-operative DWI-MRI lesion and those without.

Figure 5- 3 Boxplot representation of the baseline and the 6-month quality of life measures and 6MWT distance in patients with and without new perioperative cerebral embolic infarction.



Data are presented as median(IQR1-IQR3).
DWI=diffusion-weighted magnetic resonance imaging; EQ-5D-5L=EuroQoL-5 dimensions questionnaire; MV=mitral valve; VAS=visual analogue scale; 6MWD=six-minute walking distance.

Table 5- 5 Comparison of impact of perioperative cerebral infarction on change in health-related quality of life and functional capacity at 6 months after MV surgery, and the subgroups of MV repair and MV replacement.

	MV Surgery DWI+ve n=15	MV Surgery DWI-ve n=27	p-value	MV Repair DWI+ve n=7	MV Repair DWI-ve n=17	p-value	MV Replacement DWI+ve n=8	MV Replacement DWI-ve n=10	p-value
Change in EQ-5D-5L index	0.10((-0.04)-0.21)	0.10(0.01-0.20)	0.62	0.13((-0.02)-0.19)	0.13(0.02-0.23)	0.75	0.11±0.23	0.09±0.14	0.85
Change in VAS score	14(0-35)	10(5-30)	0.85	15(10-50)	10(9-28)	0.39	8±14	9±21	0.93
Change in 6MWD	70(25-120)	30((-10)-70)	0.10	70(30-140)	30((-10)-59)	0.24	81±86	33±60	0.21

Data are presented as mean±SD, median(IQR1-IQR3) and n(%). DWI=diffusion-weighted magnetic resonance imaging; EQ-5D-5L=EuroQoL-5 dimensions questionnaire; MV=mitral valve; VAS=visual analogue scale; 6MWD=six-minute walking distance.

5.4.5 Association of demographic and procedural factors with silent cerebral infarction

For patients undergoing MV surgery, **Table 5-6** shows the association between demographic and procedural factors and silent cerebral infarction by multiple linear regression analysis. There were no univariate factors significantly associated with the number of new cerebral infarcts; association of atrial fibrillation approached the level of statistical significance (p=0.055). There were also no significant factors independently associated with silent cerebral infarction, when variables with a p-value of <0.1 were entered into the mixed selection stepwise regression analysis.

Table 5- 6 Factors associated with the number of new cerebral infarcts in patients undergoing MV surgery by (A) multiple linear regression analysis and (B) stepwise regression analysis for variables with a p-value <0.1.

(A) Variable	Beta coefficient	p-value
Age (years)	0.02	0.64
BMI (kg/m^2)	0.06	0.54
EuroSCORE II	0.41	0.09
6-minute walking distance (m)	-0.01	0.14
Hypertension	-0.04	0.96
Type 2 Diabetes Mellitus	2.94	0.15
Atrial fibrillation	-1.77	0.055
Prior stroke/TIA	1.60	0.43
Creatinine (µmol/L)	-0.01	0.73
Haemoglobin (g/L)	0.03	0.30
Cumulative bypass time (min)	0.02	0.25
Cumulative cross clamp time (min)	-0.01	0.53

(B) Variable	Coefficient	T-value	p-value
EuroSCORE II	0.28	1.45	0.14

BMI=body mass index; EuroSCORE=European System for Cardiac Operative Risk Evaluation; MV=mitral valve; TIA=transient ischaemic attack.

5.4.6 Clinical outcomes

'Watchful Waiting' vs. MV Surgery

The median follow-up in the 'watchful waiting' and MV surgery group was similar (39(13-64) months vs. 40(12-54) months, respectively; p=0.35). There was no statistically significant difference in the MACE composite between the 'watchful waiting' group and the MV surgery group, although a higher proportion of patients in the 'watchful waiting' suffered a MACE event. Of interest, more patients died in the 'watchful waiting' group, compared to those in the MV surgery group (n=6(22%) vs. n=2(4%), respectively; p=0.02); however there were no significant differences between the other MACE components **(Table 5-7).**

MV Repair vs. MV Replacement

The median duration of follow-up in the MVr group was 32(11-44) months, whereas in the MVR group was longer 49(17-63) months; p=0.04. There was no significant difference in the MACE composite or the individual MACE components between these two surgical groups **(Table 5-7).**

Table 5- 7 Comparison of MACE outcomes between 'Watchful Waiting' group vs. MV Surgery and following MV Repair vs. MV Replacement.

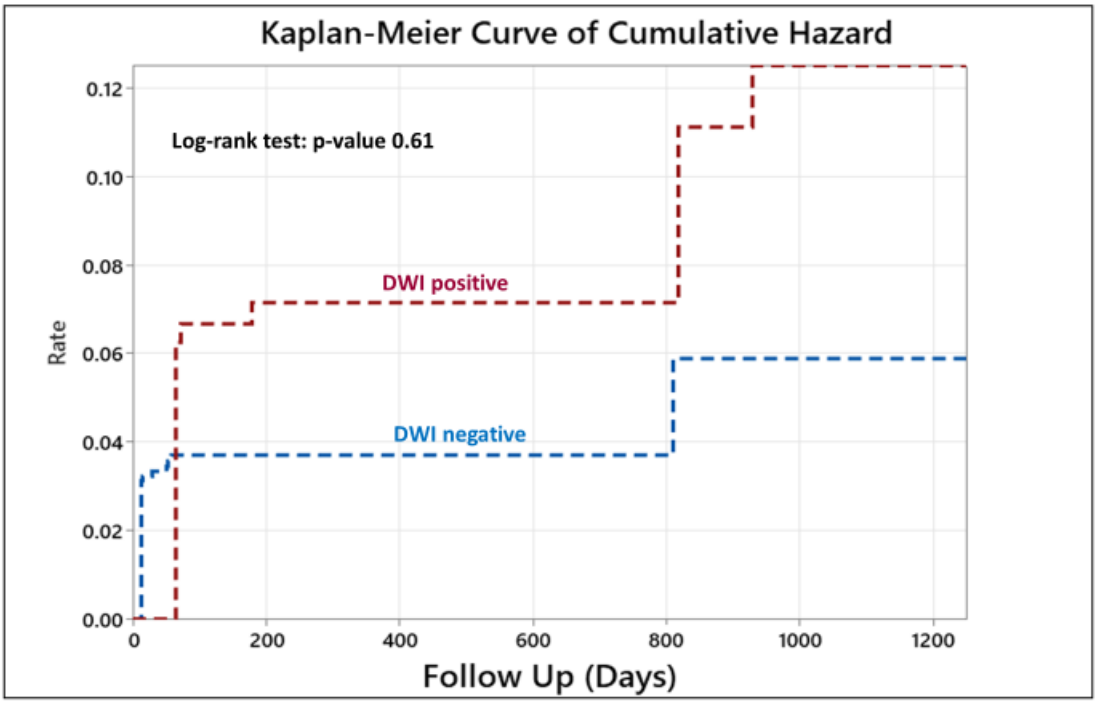
Variable	**Watchful Waiting n=27**	**MV Surgery n=50**	**p-value**	**MV Repair n=29**	**MV Replacement n=21**	**p-value**
MACE, n(%)	11(40.7)	14(28)	0.31	9(31)	5(23.8)	0.75
Death, n(%)	6(22.2)	2(4)	**0.02**	2(6.9)	0(0)	0.50
Myocardial Infarction, n(%)	1(3.7)	0(0)	0.35	0(0)	0(0)	-
Stroke/TIA, n(%)	1(3.7)	4(8)	0.65	2(6.9)	2(9.5)	1
Hospitalisation due to HF, n(%)	4(14.8)	5(10)	0.71	3(10.3)	2(9.5)	1
Acute presentation due to arrhythmia, n(%)	3(11.1)	5(10)	1	3(10.3)	2(9.5)	1
Follow-up duration (months)	39(13-64)	40(12-54)	0.35	32(11-44)	49(17-63)	**0.04**

Data are presented as median(IQR1-IQR3) and n(%). HF=heart failure; MACE=Major Adverse Cardiovascular Events; MV=mitral valve; TIA=transient ischaemic attack.

DWI positive MV Surgery vs. DWI negative MV Surgery

The MACE probability in patients undergoing MV surgery (DWI +ve vs. DWI -ve) was further evaluated by Kaplan-Meier curve of cumulative hazard. Although there is a separation of curves, with a higher rate of MACE events in the DWI+ve group, this was not statistically significant (p=0.61) **(Figure 5-4).**

Figure 5- 4 Kaplan-Meier curve for MACE probability in patients undergoing MV surgery.



DWI=diffusion-weighted magnetic resonance imaging; MACE=Major Adverse Cardiovascular Events; MV=mitral valve.

5.5 Discussion

To our knowledge, this is the first study, which evaluated the incidence of perioperative silent cerebral infarction in patients undergoing mitral valve surgery. This study demonstrated, that silent cerebral infarction is common in mitral valve surgery and affects over a third of patients. There was, however, no significant difference in the incidence between patients who underwent mitral valve repair and those who had mitral valve replacement, although the proportion of patients with a new infarct was higher in the MVR group. The infarct characteristics were overall similar between these two groups, although the volume per infarct was also higher in patients with MVR. Functional capacity and medium-term health-related quality of life improved in the surgical patients with and without new infarction, with no significant difference in the degree of improvement amongst the MV surgery patients, those with MVr or MVR. We did not find any univariate factors, which were associated with the number of new cerebral infarcts. Finally, there was no significant difference in the MACE rate between the surgical patients who had new cerebral infarction and those who did not.

5.5.1 Perioperative silent cerebral infarction in MV surgery

Stroke is a recognised complication of cardiac surgery and although uncommon, it is associated with devastating consequences.(84) Perioperative silent cerebral infarction has been shown to occur far more frequently than overt stroke(135), but its clinical implications remain unknown. As these infarcts tend to be small, numerous and multi-territorial, they are likely to be embolic in nature. Transcranial Doppler studies showed that these emboli originate from aortic cannulation, cardio-pulmonary bypass

and cross-clamping of the aorta, amongst others. The aetiology of these emboli is thought to be multifactorial, including fat, air bubbles and platelets.(89) Prior studies demonstrated large heterogeneity with regard to the incidence of acute perioperative infarction in cardiac surgery. These studies included predominantly patients undergoing isolated coronary artery bypass grafting(88), surgical aortic valve replacement(91, 92), mixed cohorts (bypass and/or valve surgery)(87, 93) or transcatheter aortic valve implantation(90, 95). To date, however, there are limited data regarding the incidence and characteristics of perioperative cerebral infarction in mitral valve surgery. Our study is, therefore the first to report the incidence of perioperative infarction in patients who underwent mitral valve surgery for mitral regurgitation and found neuro-imaging evidence of silent cerebral infarction in 36% of patients. As expected, these lesions were predominantly multiple and bilateral, which is consistent with their presumed embolic origin. Previous studies demonstrated very discordant results, with reported incidence varying from almost 20% in isolated bypass surgery(88) to over 70% in surgical aortic valve replacement(91) and almost 80% in transcatheter aortic valve implantation patients(90, 92, 95). Moreover, the results differed even in the same type of surgery, with incidence of almost 20% to 45% in bypass patients(88, 96) and from 43% to over 70% in surgical aortic valve replacement(91, 92). While there is a lot of discrepancy between the individual studies owing to different surgical techniques and population characteristics, a recent meta-analysis of almost 1500 patients who underwent on-pump cardiac surgery, reported a pooled silent cerebral infarction rate of 37%, which is in line with our findings in MV surgery.(140)

5.5.2 Perioperative silent cerebral infarction in MVr vs. MVR

Despite over a half of the patients who underwent MVR in our study having new cerebral infarction and only a quarter of patients who had a repair, there was no statistically significant difference in the incidence between these two groups. Furthermore, when the characteristics of the infarctions were compared between those patients who did have a new acute lesion, there were no substantial differences with regard to the cerebral territory, number of lesions per patient or the infarct volume per patient. The volume per infarct, however, was significantly higher in patients who underwent MV replacement. Interestingly, although a small number of previous studies did include patients undergoing MV surgery as part of their valvular cohorts, the reported results did not differentiate between patients who underwent MV surgery and those with other valvular operations.(85, 87, 93, 135) Moreover, no prior study examined the differences in the perioperative infarction between MV repair and replacement. The findings of our study are reassuring, as while there were no major differences between the groups, the incidence of acute infarction was numerically lower in patients who underwent repair. This is important, as current guidelines recommend mitral valve repair rather than replacement, whenever feasible.(1)

5.5.3 Functional and health-related quality of life outcomes

As post-operative neurocognitive dysfunction is very common, particularly following cardiac surgery, the majority of prior studies aimed to evaluate whether this was driven by perioperative cerebral infarction. Although some studies found an association between an early post-operative neurocognitive dysfunction and cerebral infarction(85, 88), the majority of studies found no

significant impact on cognitive function at later follow-up(86, 87). Only a minority of studies, however, assessed quality of life in patients with new cerebral infarction. These studies, which included primarily patients undergoing transcatheter aortic valve implantation and surgical aortic valve replacement(90, 92), found no impact on the short- or medium-term quality of life. This is important to consider in mitral valve surgery, as a large proportion of patients undergo mitral valve repair for a prognostic, rather than a symptomatic benefit. In our study, as expected, there was a significant improvement in the quality of life measures and the 6-minute walking distance in patients who underwent MV surgery, with no change in the ‘watchful waiting’ group. Furthermore, when the post-operative change in the quality of life was examined between the patients with new infarction and those without, there was no significant difference in the improvement between these 2 groups at 6-months. This was subsequently evaluated separately in the repair and replacement groups, with concordant results.

5.5.4 Factors associated with new infarction

Multiple linear regression analysis did not reveal any clinical or operative variables which associated with the number of new lesions. Only atrial fibrillation and EuroSCORE II approached statistical significance. Furthermore, subsequent mixed selection stepwise regression analysis did not identify any independent factors. This is in contrast to prior surgical studies, which found an association with aortic arch atheroma in transcatheter aortic valve implantation and with concomitant coronary artery bypass grafting in surgical aortic valve replacement.(92) A large meta-regression analysis identified advanced age and diabetes as risk factors for

silent cerebral infarction after on-pump surgery, while lower risk was shown in isolated coronary artery bypass graft.(140) It is important to note, however, that the prevalence of co-morbidities in our population was very low. This may explain why we did not find any factors associated with the number of new lesions.

5.5.5 MACE rates

While small cerebral infarction in the general population may be associated with an increased risk of adverse clinical outcomes, such as stroke and excess mortality(141), this was not observed in our study. With regard to the rate of MACE, there was separation of Kaplan-Meier curves between the patients with new DWI lesions and those without, however, this was not statistically significant. While new, silent cerebral infarction did not have a negative effect on clinical outcomes in our study, it is important to note that silent cerebral infarction in the general population can be associated with cognitive decline. As assessment of cognitive function requires specialised neurocognitive testing, which was not performed in our study, the impact of silent cerebral infarction in mitral valve surgery on long-term cognitive function remains unknown.

5.5.6 Limitations

This was an exploratory, single-centre observational cohort study, with a median follow-up of over 3 years. While the cerebral MRI scans were performed at a 1.5T strength, which is sufficient for detection of new cerebral infarction, higher field strengths may have greater sensitivity.(142) The study had a potential for bias, as only patients who were clinically stable and required elective surgery were recruited. In addition to survivor bias, patients

who had prolonged recovery or were very frail postoperatively would be less likely to undergo study assessments. The sample size was limited to detect differences between MVr and MVR, but has provided novel insights into the incidence and impact of silent cerebral infarction after mitral valve surgery in general. The outcomes in our study were focused on patient reported quality of life and cardiovascular outcomes, rather than detailed neurocognitive assessment. As such, although our study did not demonstrate a significant impact of new silent cerebral infarction on quality of life and MACE rates, their influence on subtle neurocognitive function remains unknown.

5.6 Conclusions

To our knowledge, this is the first study that evaluated new silent cerebral infarction in patients undergoing mitral valve surgery. Mitral valve replacement compared to repair had proportionally but not significantly greater incidence of perioperative silent cerebral infarction. Our study showed no significant differences between the majority of infarct characteristics between patients undergoing mitral valve repair and mitral valve replacement, although volume per infarct was larger in the replacement group. As expected, improvement of health-related quality of life and functional capacity was seen at the 6-month follow-up in the surgical patients. Furthermore, the degree of improvement was not attenuated by the presence of silent cerebral infarction nor did it impact on the rate of MACE during follow-up.

Chapter 6
Thesis Conclusions

6.1 The role of CMR in the assessment of left and right ventricular volume and function is well established. Although CMR is not the first-line modality for the assessment and quantification of primary mitral regurgitation, there is growing body of evidence to suggest that TTE may be insufficient in the majority of patients with this particular pathology. Several studies to date have shown its diagnostic and prognostic advantages.

TTE is frequently suboptimal, due to patients' characteristics and poor acoustic windows, but also because PISA measurements are solely based on a single systolic frame, which does not accurately represent the MR severity throughout the cardiac cycle. Previous studies have extensively demonstrated, that PCMR assessment of primary MR is more accurate as it is independent of patient's body habitus, jet eccentricity, systolic duration and the presence of multiple jets. These aforementioned studies demonstrated that regurgitant volumes quantified by PCMR were associated with post-operative LV reverse remodelling, while TTE-quantified regurgitant volumes were not. This is particularly important in the asymptomatic patients, who undergo surgery solely for prognostic reasons. While several studies utilised the novel 4DF CMR to quantify mitral regurgitation volume and have shown that there is a good agreement between PCMR and 4DF CMR, no studies to date evaluated if 4DF CMR assessment of MR volume is also associated with post-operative LV remodelling, in the same was as

PCMR. As 4DF CMR presents a number of advantages, due to its free-breathing and relatively rapid acquisition, it was important to evaluate whether the regurgitant volumes obtained with this technique are also associated with post-operative LV reverse remodelling. As this has never been looked at before, our study is the first study to suggest the presence of this association. This adds to the already available and growing body of evidence for the utility of 4DF CMR in the assessment of primary MR. 4DF CMR may be useful not only as an add-on to a standard PCMR protocol, but it can be used in isolation in patients unable to tolerate the standard PCMR scan.

Exercise echocardiography is currently the exercise imaging modality of choice. It is however bound by several limitations, and possibly not feasible in large proportion of patients with primary MR. Studies have shown, that frequently it is impossible to quantify MR by TTE during exercise due to poor image quality. We know, however, that assessment of MR during exercise has diagnostic and prognostic advantages. Absence of cardiac reserve or the development of pulmonary hypertension during exercise have been shown to be associated with adverse outcomes. However, the limited utility and reproducibility of exercise-TTE have led to the development of exercise-CMR. The feasibility and reproducibility of exercise-CMR in the assessment of biventricular volumes and aortic flow have been previously demonstrated in healthy volunteers. The superior accuracy and reproducibility of CMR at rest make EX-CMR appealing as the imaging modality of choice. Previous studies have mainly utilised EX-CMR in the assessment of ischaemia and

congenital heart disease. Early studies in valvular heart disease applied EX-CMR to aortic regurgitation. No studies to date, however, demonstrated the feasibility or reproducibility of EX-CMR in the assessment of asymptomatic patients of primary MR. Our study has documented not only the feasibility and reproducibility of MR assessment during EX-CMR in this group of patients, but also, for the first time, we described the response of mitral regurgitant volume and fraction during EX-CMR. While this was a feasibility study, and no clinical outcomes were assessed, the variable individual response of MR to exercise suggest the need for a larger clinical trial and establishment of association with clinical outcomes.

Each of the two techniques described above brings with itself a whole array of advantages in the assessment of MR. Therefore, we attempted to combine these 2 techniques, which led to the attempt of 4DF-CMR in exercise pulse sequence development. No studies to date, have performed this successfully during continuous in-scanner exercise. While our 4DF-CMR in exercise pulse sequence development has not be successful, we have managed to advance 4DF-CMR imaging in exercise, as the acquisition became possible even at moderate-intensity heart rate, with excellent image quality in one volunteer. This holds promise for further developments.

Lastly, we evaluated the incidence and characteristics of silent cerebral infarction in mitral valve surgery. We know from prior studies that silent cerebral infarction is much more common in cardiac surgery than overt stroke, but its clinical consequences including impact on cognitive function and quality-of-life remain unclear. Some of the prior studies include patients undergoing mitral valve surgery, either replacement or repair, however these

patients constituted by far the minority of patients in these study populations and no conclusions could be drawn about the incidence or characteristic of silent cerebral infarction in these patients. Until now, there were no dedicated studies, which evaluated SCI in this particular group of patients. It was important to evaluate this, as prior studies in other cardiac surgeries and TAVI suggested a possible impact on quality-of-life and cognitive function. This is especially important in younger patients undergoing MV surgery for prognostic reasons in the absence of symptoms. Our study was, therefore, the first study dedicated to assess the incidence and characteristics of SCI in mitral valve surgery, describe the differences between repair and replacement and evaluate the impact on clinical outcomes. We have shown, that while SCI is indeed quite common in mitral valve repair, there are no significant difference in the incidence and characteristics of SCI between mitral valve repair and mitral valve replacement. In our study, the presence of SCI was not associated with increased MACE rate and reduced medium-term quality of life or functional capacity. While this was a small study with only medium-term follow up and no assessment of cognitive function, it did demonstrate, for the first time, the incidence and significance of SCI in mitral valve surgery.

6.2 Future directions

Although all our studies were small, observational and single-centre, and the results have to be confirmed in larger clinical trials, we do believe we have added to the growing body of evidence for the utility of 4DF-CMR and EX-CMR in the future clinical practice.

Possible future directions for these areas of research include establishment of correlation of the 4DF-CMR-derived mitral regurgitant volume with long-term clinical outcomes in a larger number of patients undergoing mitral valve surgery for primary MR. With regard to EX-CMR, it would be important to correlate the response of MR volume to exercise i.e. increase or decrease during exercise, with clinical outcomes in order to establish diagnostic algorithm, which would allow guiding timely surgical therapy decisions in the asymptomatic patients. Further attempts are needed in order to achieve a working and clinically useful 4DF CMR in exercise pulse sequence. This would require piloting different sequences with careful optimisation of all the key parameters, on different field strength and with different vendors. Lastly, as our study of SCI in mitral valve surgery did not address long-term clinical outcomes or the impact of SCI on cognitive function, larger clinical trials are needed to establish these relationships.

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Abbreviations

2D=two-dimensional

3D=three-dimensional

4DF=four-dimensional flow

4DF-CMR=4-dimensional flow cardiovascular magnetic resonance imaging

6MWT=six-minute walk test

AFF=aortic forward flow

CI=confidence interval

CMR=cardiovascular magnetic resonance

CPEX=cardio-pulmonary exercise test

C-SENSE=compressed-SENSE

DWI-MRI=diffusion-weighted magnetic resonance imaging

EQ-5D-5L=EuroQoL 5-dimensions questionnaire

EX-CMR=exercise cardiovascular magnetic resonance

EX-TTE=exercise transthoracic echocardiography

HRR= heart rate reserve

ICC=intra-class correlation coefficient

Low-EX=low-intensity exercise stage

LV=left ventricle

LVEDV= left ventricle end-diastolic volume

LVEF = left ventricular ejection fraction

LVOT = left ventricular outflow tract

LVSV= left ventricle stroke volume

MACE=Major Adverse Cardiovascular Events

Mod-EX=moderate-intensity exercise stage

MR=mitral regurgitation

MRI=magnetic resonance imaging

MR-Rvol=mitral regurgitant volume

MV=mitral valve

MVr=mitral valve repair

MVR=mitral valve replacement

PCMR=phase contrast magnetic resonance

PISA=proximal isovelocity surface area

PSD=pulse sequence development

RVT=retrospective valve tracking

SCI=silent cerebral infarction

SFT=semi-automated flow tracking

SNR=signal-to-noise ratio

SV=stroke volume

TR=tricuspid regurgitation

TTE=transthoracic echocardiography

TV=tricuspid valve

VENC=velocity encoding

VHD=valvular heart disease

WW=watchful waiting

Appendix A Ethical approval, patient information sheet and consent form for Chapters 2 & 5

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

Telephone: 0191 4283548

24 December 2015

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

Dear Professor Greenwood

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

Thank you for your letter of 21st December 2015, responding to the Committee's request for further information on the above research and submitting revised documentation.

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

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to make a request to postpone publication, please contact the REC Manager, Ms Gillian Mayer, nrescommittee.yorkandhumber-southyorks@nhs.net.

Confirmation of ethical opinion

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

Conditions of the favourable opinion

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

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

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

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

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

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

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

Registration of Clinical Trials

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

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

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

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

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

Ethical review of research sites

NHS sites

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

Approved documents

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

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

Statement of compliance

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

After ethical review

Reporting requirements

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

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

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

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Training

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

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

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

Yours sincerely

pp

Dr Ian Woolands
Chair

Email:nrescommittee.yorkandhumber-southyorks@nhs.net

Enclosures: "After ethical review – guidance for researchers"

Copy to: *Faculty Research and Governance Administrator*

Anne Gowing, Leeds Teaching Hospitals NHS Trust

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

Tel: 0207 104 8079

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

28 February 2019

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

Dear Ms Bijsterveld

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

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

Summary of Amendment

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

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

Ethical opinion

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

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

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

It was suggested a flow diagram would be helpful.

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

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

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

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

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

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

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

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

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

Approved documents

The documents reviewed and approved at the meeting were:

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

Membership of the Committee

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

Working with NHS Care Organisations

Sponsors should ensure that they notify the R&D office for the relevant NHS care organisation of this amendment in line with the terms detailed in the categorisation email issued by the lead nation for the study.

Statement of compliance

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

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

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

Yours sincerely
Pp

Dr Max Huxham
Chair

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

A Research Ethics Committee established by the Health Research Authority

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

MRI-MVR-TVR (pilot study)

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

Participant Information Leaflet

Version 2.3 January 14 2019

Chief Investigator: Prof John Greenwood

Dear patient,

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

WHY HAVE I BEEN CHOSEN?

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

WHAT IS THE PURPOSE OF THE STUDY?

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

If you are having your mitral valve replaced we would also like to study the blood vessels in the head. As your doctor will have told you one of the risks of valve replacement is small clots travelling from the heart to the head. It is important for us to find out how often this happens with surgery and with non-surgical replacement, and compare the results. We will use Magnetic Resonance Imaging (MRI) in this study to look at the head and the heart. MRI does not involve radiation and is therefore very safe. It gives us very good images of the blood vessels and can tell how well the heart is pumping.

DO I HAVE TO TAKE PART?

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

WHAT WILL HAPPEN TO ME IF I TAKE PART?

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

You will also have an echocardiogram (ultrasound scan of the heart) at the beginning of the study and again after 6 months, and at the same time points we will do a 6 minute walk test with you (where we see how far you can walk in 6 minutes).

If you are having tricuspid valve treatment we will also measure your ankles to see if they are swollen.

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

Finally we will take a blood sample (to measure your kidney function, to check for anaemia and to look at markers of heart strain) from you at each of the two visits. If you are having tricuspid valve treatment we will also measure your

liver function. We will use the cannula that we use to give you the MRI contrast dye, so it does not involve any extra needles.

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

WHAT ARE THE RISKS AND DISCOMFORTS?

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

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

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

With your permission your stored sample may be used in future heart related research studies.

BENEFITS TO YOU

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

EXPENSES

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

WILL MY TAKING PART BE KEPT CONFIDENTIAL?

All information collected about you during the course of the study will be kept strictly confidential. This information will be securely stored, electronically on the Leeds Teaching Hospitals NHS Trust secure server, on the University of Leeds secure server, and on paper, under the provisions of the 2018 Data Protection Act. The data collected will be coded and your personal details will be kept separately. You will not be identified in any publication that may result from this research. With your permission, we will inform your GP of your participation in the study. If any unexpected abnormality or condition were found we would inform your GP. If you withdraw consent from further study follow-up, or if you were to become incapacitated, any data collected about you up to that point will remain on file and will be included in the final study analysis.

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

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

When you agree to take part in a research study, the information about your health and care may be provided to researchers running other research studies in this organisation and in other organisations. These organisations may be universities, NHS organisations or companies involved in health and care research in this country or abroad. Your information will only be used by organisations and researchers to conduct research in accordance with the UK Policy Framework for Health and Social Care Research**.**

This information will not identify you and will not be combined with other information in a way that could identify you. The information will only be used for the purpose of health and care research, and cannot be used to contact you or to affect your care. It will not be used to make decisions about future services available to you, such as insurance.

WHAT WILL HAPPEN IF THERE ARE UNEXPECTED ABNORMALITIES ON MY SCAN?

Occasionally abnormalities that were not expected are picked up on the head and heart scans, blood tests or ultrasound heart scan (echocardiogram). If this is the case we will inform both your treating Consultant and your GP, and they will arrange further investigation if they feel that this is necessary.

WHAT WILL HAPPEN TO THE RESULTS OF THE RESEARCH STUDY?

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

INDEMNITY/COMPENSATION

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.

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

Hospital Number: ..... Initials: .....

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

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

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

Appendix B Ethical approval, patient information sheet and consent form for Chapters 3 & 4

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

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15 June 2018

Dear Professor Plein

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

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

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

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

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

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

IRAS project ID	245109

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

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

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

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

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

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

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

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

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

The sponsor contact for this application is as follows:

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

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

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

IRAS project ID	245109

Yours sincerely

Thomas Fairman
HRA Assessor

Email: hra.approval@nhs.net

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

IRAS project ID	245109

List of Documents

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

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

IRAS project ID	245109

Summary of assessment

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

Assessment criteria

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

IRAS project ID	245109

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

Participating NHS Organisations in England and Wales

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

IRAS project ID	245109

Principal Investigator Suitability

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

HR Good Practice Resource Pack Expectations

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

Other Information to Aid Study Set-up

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

PARTICIPANT INFORMATION SHEET - PATIENTS
Version 1.2 –October 04 2018

AMaRI

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

Chief Investigator: Professor Sven Plein

Dear Patient,

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

Purpose of the study

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

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

Why have I been chosen*?*

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

Do I have to take part?

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

What will happen to me if I take part?

Most patients will have a single MRI scan. A small group of participants in this study will be asked to undergo up to four MRI scans to allow comparisons between different ways of obtaining MRI pictures. It is entirely up to you how many scans you wish to volunteer for, and you will remain free to withdraw from the study at any time. All scans will be performed at the Leeds General Infirmary, and will be performed on separate days.

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

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

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

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

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

We may ask you to come for the scan in a fasted state, or offer to scan you following a meal which we will provide you with, so that we can assess the influence of fed or fasted state on the heart scan assessments.

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

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

Risks and discomforts

Magnetic Resonance Imaging (MRI) is safe and no x-rays or radiation are used for this scan. There are no known risks from this technique. Some people may experience claustrophobia. Our MRI staff will do all that they can to make you feel comfortable during the scan, and will be monitoring you via a video camera and an audio link. If we are unable to make you feel comfortable in the scanner, we will not go ahead with scanning. You may experience minor bruising or irritation at the site where we place the cannula in your arm.The contrast medication which we use is very safe but, as with any injection, reactions may occur. These include a warm sensation at the injection site, nausea or vomiting and transient skin rash. These effects usually only last for a few minutes. People with a history of allergy are more likely to suffer a more

severe reaction, but this is rare (less than 1 in 3000). The department is equipped to cope with allergic reactions if they happen. Adenosine, the medication we use to increase the blood flow to the heart, can cause flushing, breathlessness and chest discomfort. However, all of these feelings usually subside within one or two minutes or even more quickly if the medication is stopped. Immersing your hands or feet in cold water is unpleasant, but the effects wear off very quickly. Nitrates and a beta blocker can cause temporary light headedness. For this reason if these drugs are used you will be kept under observation until the effects have worn off.

Benefits to you

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

Expenses

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

Will my taking part be kept confidential?

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

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

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

The University of Leeds is the sponsor for this study based in the United Kingdom. We will be using information from you and/or your medical records in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. The University of Leeds and the Leeds Teaching Hospitals NHS Trust (on behalf of the University of Leeds), will keep identifiable information

about you for the purpose of the study for a maximum of 15 years after the study has finished. Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible.

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

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

What will happen to the results of the research study?

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

Indemnity/Compensation

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

The research organisation

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

CONSENT FORM v 1.2 October 04 2018

AMaRI

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

Chief Investigator: Professor Sven Plein

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

Patient initials ……

Please initial boxes

1. I have read the Patient Information Sheet dated October 042018 (Version 1.2) for the above study and I have had the opportunity to ask questions and discuss the research study and I am satisfied with the answers to my questions. ☐

2. I have received enough information about this study. ☐

3. I understand that my participation is voluntary and that I am free to withdraw from the study at any time without giving a reason. ☐

4. I give my consent for my General Practitioner to be informed in the event of any abnormality being discovered and that the cardiologist will be informed only if we find any abnormality over and above which is already known. ☐

5. I understand that images collected will be stored on an NHS computer system, and, after my personal details have been removed, may be available to researchers at other institutions in the UK, the EEA, and countries outside the EEA. ☐

6. I understand that some of the blood samples taken from me may be ☐

stored and may be analyzed in the future for markers related to heart disease

7. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from the University of Leeds, from regulatory authorities, or from the Leeds Teaching Hospitals NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

8. If I were to lose capacity, I understand that data already collected will be kept and used for the purposes of the study. ☐

9. I agree to take part in this research study and that the general results of the study will be made available to the medical community most likely through publication in a reputable medical journal. ☐

10. I am willing to be contacted again in the future to receive information about the publication of this study. Yes ☐ No ☐

11. I am willing to be contacted again in the future with regard to potentially taking part (without any obligation) in further related research studies, or attending for further MRI scans. Yes ☐ No ☐

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

Signature.....

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

Signature of researcher.....

Name (block capitals).....Date……