RESEARCH ARTICLE

4D Flow Cardiac MR in Primary Mitral Regurgitation

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Background: Four-dimensional-flow cardiac MR (4DF-MR) offers advantages in primary mitral regurgitation. The relationship between 4DF-MR-derived mitral regurgitant volume (MR-Rvol) and the post-operative left ventricular (LV) reverse remodeling has not yet been established.
Purpose: To ascertain if the 4DF-MR-derived MR-Rvol correlates with the LV reverse remodeling in primary mitral regurgitation.
Study Type: Prospective, single-center, two arm, interventional vs. nonintervention observational study.
Population: Forty-four patients (male N = 30; median age 68 [59–75]) with at least moderate primary mitral regurgitation; either awaiting mitral valve surgery (repair [MVr], replacement [MVR]) or undergoing "watchful waiting" (WW).
Field Strength/Sequence: 5 T/Balanced steady-state free precession (bSSFP) sequence/Phase contrast imaging/Multishot echo-planar imaging pulse sequence (five shots).
Assessment: Patients underwent transthoracic echocardiography (TTE), phase-contrast MR (PMRI), 4DF-MR and 6-minute walk test (6MWT) at baseline, and a follow-up PMRI and 6MWT at 6 months. MR-Rvol was quantified by PMRI, 4DF-MR, and TTE by one observer. The pre-operative MR-Rvol was correlated with the post-operative decrease in the LV end-diastolic volume index (LVEDVi).
Statistical Tests: Included Student *t*-test/Mann–Whitney test/Fisher's exact test, Bland–Altman plots, linear regression analysis and receiver operating characteristic curves. Statistical significance was defined as $P < 0.05$.
Results: While Bland–Altman plots demonstrated similar bias between all the modalities, the limits of agreement were narrower between 4DF-MR and PMRI (bias 15; limits of agreement −36 mL to 65 mL), than between 4DF-MR and TTE (bias −8; limits of agreement −106 mL to 90 mL) and PMRI and TTE (bias −23; limits of agreement −105 mL to 59 mL). Linear regression analysis demonstrated a significant association between the MR-Rvol and the post-operative decrease in the LVEDVi, when the MR-Rvol was quantified by PMRI and 4DF-MR, but not by TTE ($P = 0.73$). 4DF-MR demonstrated the best diagnostic performance for reduction in the post-operative LVEDVi with the largest area under the curve (4DF-MR 0.83; vs. PMRI 0.78; and TTE 0.51; $P = 0.89$).
Data Conclusion: This study demonstrates the potential clinical utility of 4DF-MR in the assessment of primary mitral regurgitation.
Evidence Level: 2
Technical Efficacy: Stage 5

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When untreated, severe mitral regurgitation is associated with excess morbidity and mortality.[1] 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.[2] Guidelines recommend transthoracic echocardiography (TTE) as the first-line modality for quantification of mitral regurgitation.[3,4] 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.[5]

Phase-contrast magnetic resonance imaging (PMRI) imaging provides an advantage in these challenging cases and enables not only an accurate evaluation of mitral regurgitation severity, but also its impact on left ventricular (LV) size and function.[6] Prior studies have showed a poor correlation between mitral regurgitation quantification by PMRI and TTE, primarily in patients with eccentric, multiple or late-systolic jets, which are inherent in degenerative mitral regurgitation, and demonstrated a prognostic advantage of PMRI.[7,8] Four-dimensional flow magnetic resonance imaging (4DF-MR) is a technique that allows 3-dimensional and time-relative assessment of flow across all four valves within one, simple, free-breathing acquisition.[9] In contrast to PMRI, 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.[10] Studies which compared 4DF-MR and PMRI, showed that the assessment of mitral regurgitation by 4DF-MR was feasible and reproducible, with 4DF-MR having better intra- and inter-observer reproducibility than PMRI.[11,12] Moreover, it remained accurate even in the presence of atrial fibrillation.[13] Although 4DF-MR is constrained by background phase-offset errors, limited temporal and spatial resolution, and laborious post-processing, it has the potential to become the reference-standard in the assessment and quantitation of mitral regurgitation.[9]

Current guidelines recommend mitral valve repair rather than replacement, if feasible.[3,4] This is, however, based on observational studies, which suggest a survival advantage with this approach. The development of new surgical techniques, that allow chordal preservation may in fact improve the LV reverse remodeling following MVR.[14–16]

To our knowledge, there are no studies which have examined the relationship between the 4DF-MR-derived pre-operative mitral regurgitation volume with the post-operative LV reverse remodeling in primary mitral regurgitation. Therefore, this study aimed to determine the agreement between 4DF-MR-derived mitral regurgitant volume with PMRI- and TTE-derived mitral regurgitant volume, and to ascertain if the 4DF-MR-derived mitral regurgitant volume is associated with the post-operative LV reverse remodeling in primary mitral regurgitation.

Methods

Study Design and Population

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. This was a prospective, single-center, 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 those who were undergoing "watchful waiting" (WW). Therapeutic decisions were made by the multi-disciplinary heart team in accordance with the European Society of Cardiology guidelines who were independent from the study. Patients who were asymptomatic and did not have indications for surgery were managed medically and underwent WW.[3]

The grading of at least moderate mitral regurgitation was confirmed by the multi-disciplinary heart team based on transthoracic and/or transesophageal echocardiography according to American Society of Echocardiography criteria.[17]

Exclusion criteria included more than mild aortic valve disease and general contraindications to MRI.

Mitral Valve Surgery

MV surgery was performed according to the standard surgical practice, including midline sternotomy, cardiopulmonary bypass technique, systemic heparinization, and mild systemic hypothermia. The procedure was performed under intra-operative transesophageal 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.

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 PMRI, 4DF-MR, TTE, and a 6-minute walk test (6MWT). The follow-up assessment was undertaken 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 PMRI and a 6MWT.

PMRI. PMRI scan protocol (1.5 T Philips Ingenia, Best, Netherlands; 32-element cardiac coil) included survey images; free-breathing transverse Half-Fourier Acquisition Single-shot Turbo spin Echo imaging; cine images acquired with breath-hold balanced steady-state free precession sequence

(4-chamber view and vertical-long axis view, 2 orthogonal left ventricular outflow tract views, 2 orthogonal right ventricular outflow views). Left ventricular short-axis stack with sequence parameters as follows: typical field-of-view 340 mm, 10 mm slice thickness with 0 mm gap, repetition time 3 msec, echo time 1.6 msec, flip angle 60°, sensitivity encoding factor 2, in-plane acquired spatial resolution 1.88 × 1.88 mm, 30 reconstructed phases and matrix 192 × 131. Transaxial right ventricular cine stack with the following sequence parameters: typical field-of-view 360 mm, 8 mm slice thickness with 0 mm gap, repetition time 2.8 msec, echo time 1.41 msec, flip angle 60°, sensitivity encoding factor 1.8, in-plane acquired spatial resolution 1.88 × 1.88 mm, 20 reconstructed phases and matrix 192 × 143. Through-plane aortic phase contrast images: planned at sino-tubular junction and orthogonal to the vessel.[18] In patients with atrial fibrillation, two acquisitions were acquired. Velocity encoding was set to 150 cm/s and increased as required. Sequence parameters: typical field-of-view 350 × 280 mm, slice thickness 8 mm, repetition time 5.1 msec, echo time 3.2 msec, flip angle 15°, temporal resolution 28 msec, number of signal averages 1, sensitivity encoding factor 2, in-plane acquired spatial resolution 2.5 × 2.5 mm, 30 reconstructed phases, phase percentage 100%, matrix 140 × 112, Cartesian sampling, turbo field echo factor 3 and acquisition duration 30.8 msec. Through-plane pulmonary phase contrast images: planned approximately 1 cm above the pulmonary valve and orthogonal to the vessel. Sequence parameters as per through-plane aortic PMRI.

PMRI IMAGE ANALYSIS. Images were analyzed blinded to clinical details using standard cvi42 software (Circle Cardiovascular Imaging, Calgary, AB, Canada) by TC (2 years of experience) and PGC (2 years of experience). LV volumes were analyzed 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.[19] Left ventricular mass was estimated by manual tracing of the epicardial and endocardial border in end-diastole.[19] Right-ventricular volumes were analyzed by manual tracing of the endocardial border in end-diastole and end-systole on the RV transaxial cine stack.[20] 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, two flow acquisitions were analyzed and the final flow volume was taken as the average of the two measurements.

PMRI MITRAL REGURGITANT VOLUME QUANTIFICATION. Mitral regurgitant volume was estimated indirectly, as follows: Mitral regurgitant volume = LV stroke volume − Aortic forward flow volume; where LV stroke volume = LV end-diastolic volume − LV end-systolic volume.[21]

4DF-MR. 4DF-MR was acquired with multishot echo-planar imaging pulse sequence (five shots). Images were planned in a transverse orientation. Sequence parameters were as follows: retrospective gating, typical field-of-view 400 mm, 39 slices, shortest repetition time, shortest echo time, flip angle 10°, 30 reconstructed phases, isotropic acquired voxel size 3 × 3 × 3 mm, Cartesian acquisition, velocity encoding 150 cm/s. The above multishot echo-planar imaging pulse sequence was previously validated by Garg and colleagues.[22]

4DF-MR IMAGE ANALYSIS. All 4DF-MR data were analyzed blinded to clinical details by MG (3 years of experience) and reviewed by MB (14 years if experience). Images were analyzed 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.[23] 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-MR MITRAL REGURGITANT VOLUME QUANTIFICATION. Mitral regurgitant volume was quantitated indirectly, where Mitral regurgitant volume = mitral forward flow volume (4DF-MR-derived) − aortic stroke volume (4DF-MR-derived). This method was chosen due to its previously demonstrated superior reproducibility and high level of precision.[12]

Transthoracic Echocardiography

TTE was performed in a standard manner as per the British Society of Echocardiography guidelines; notably, mitral regurgitation assessment included evaluation of the mitral valve and mitral regurgitant jet in the apical 4-chamber, 2-chamber, and 3-chamber view, with continuous wave Doppler assessment of the mitral jet in the 4-chamber view, which allows for measurement of maximum velocity and velocity-time-integral.[24]

TTE Mitral Regurgitant Volume Quantification

This was based on the proximal isovelocity surface area (PISA) method,[25] where Mitral regurgitant volume = effective regurgitant orifice area × velocity-time integral with EROA = $(2\pi r^2 \times$ Nyquist limit$)$/peak velocity and where r = PISA radius.

Six-Minute Walk Test

Functional exercise capacity was assessed using the 6MWT distance (m) performed in accordance with the American Thoracic Society guidelines.[26]

Clinical Outcomes

Major adverse cardiovascular events (MACEs) were defined as the composite of all-cause death, myocardial infarction, stroke/transient ischemic attack, hospitalization for heart failure and acute hospitalization for arrhythmia.

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 mitral regurgitant volume between the different modalities was compared with Bland–Altman plots. Linear regression analysis was performed to examine the association between the pre-operative mitral regurgitant volume and the post-operative reduction in the LV end-diastolic volume index. Receiver operating characteristic curves were utilized to assess the diagnostic performance of each modality; these were created by using binary logistic regression of mitral regurgitant volume calculated by the three methods and more than mean post-operative reduction in the LV end-diastolic volume index. All analyses were performed using Minitab (version 19) and statistical significance was defined as $P < 0.05$.

Results

Demographic, Clinical Characteristics, and Surgical Procedural Data

Paired assessments were completed by 44 patients, of whom 15 were in the WW (age 67 [47–80] years; male N = 9 [60%]) group and 29 in the MV surgery group (age 69 [64–72] years; male N = 21 [72.4%]) (Fig. 1).

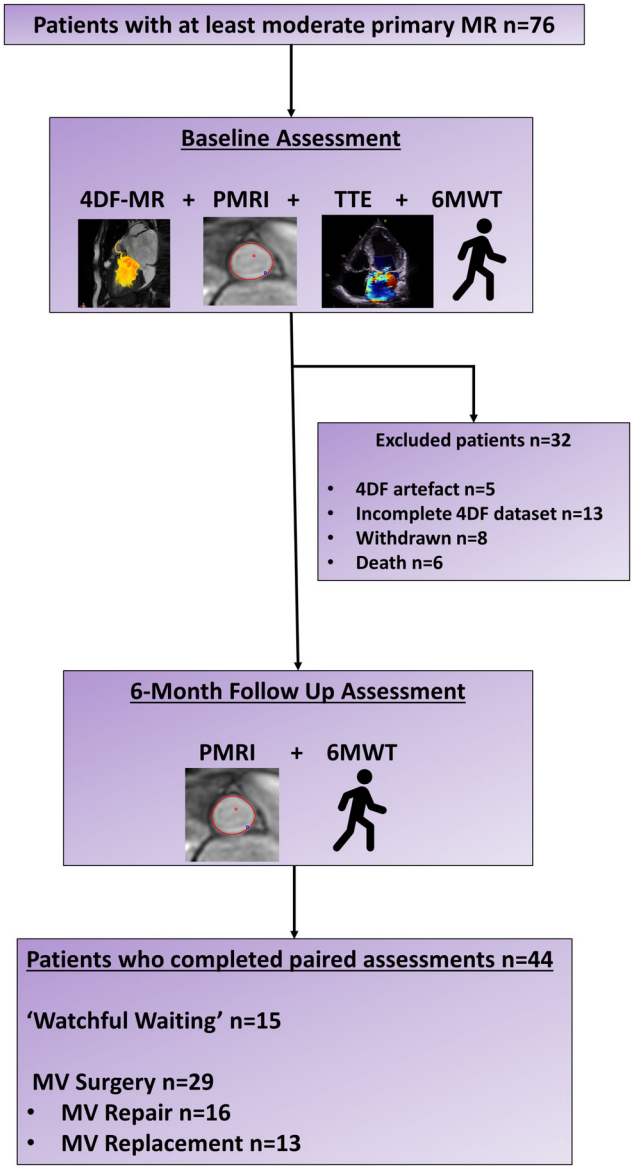

FIGURE 1: Patient flow and study assessments. 4DF-MR = 4-dimensional flow cardiac magnetic resonance imaging; 6-minute walk test = 6-minute walk test; MR = mitral regurgitation; MV = mitral valve; PMRI = phase-contrast magnetic resonance imaging; TTE = transthoracic echocardiography.

"WATCHFUL WAITING" VS. MV SURGERY. The demographic and clinical characteristics were comparable between the WW and the MV surgery group (Table 1). 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%]). The most common etiology of mitral regurgitation 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 etiology.

MV REPAIR VS. MV REPLACEMENT. There were no significant differences in the demographic or clinical characteristics between the MVr (age 68 [59–71] years; male N = 13 [81.3%]) and the MVR group (age 69 [63–74] years; male N = 8 [61.5%]) (Table 2). A significantly larger proportion of patients in the MVr group had posterior mitral valve prolapse (MVr N = 13 [81.2%] vs. MVR N = 6 [46.2%]). There were also no significant differences in the surgical procedural characteristics between these groups, in terms of cumulative bypass time (MVr 119 [100–146] minutes vs. MVR 111 [99–127] minutes) (Table 2). A small proportion of patients in both groups underwent a concomitant

TABLE 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
Hemoglobin (g/L)	135 ± 12	141 ± 9	0.07
6MWT distance (m)	355 ± 116	383 ± 81	0.41
Mitral regurgitation etiology			
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 (%). 6MWT = six-minute walk test; BMI = body mass index; COPD = chronic obstructive pulmonary disease; EuroSCORE = European System for Cardiac Operative Risk Evaluation; MI = myocardial infarction; MVP = mitral valve prolapse; NYHA = New York Heart Association; TIA = transient ischemic attack.

surgical procedure (coronary artery bypass grafting and/or tricuspid valve repair), whereas one 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%]).

Baseline Imaging Characteristics

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

"WATCHFUL WAITING" VS. MV SURGERY. With regard to the PMRI characteristics, patients in the WW group had significantly smaller mean LV end-diastolic volumes (WW 208 ± 42 mL vs. MV surgery 247 ± 72 mL), but not when indexed to body-surface area (WW 114 ± 20 mL vs. MV surgery 130 ± 34 mL; $P = 0.05$ [95% confidence interval −33.05, 0.06]). Left ventricular mass and LV mass index were both significantly lower in the WW group (LV mass WW 94 ± 22 g vs. MV surgery 123 ± 41 g and LV mass index WW 51 ± 11 g/m^2 vs. MV surgery 64 ± 16 g/m^2). There were no significant differences between the LV ejection fraction or stroke volume (LV ejection fraction WW 59 ± 6% vs. MV surgery 55 ± 8%; stroke volume 121 ± 24 mL vs. 134 ± 37 mL, respectively). The right ventricular ejection fraction was significantly higher in the WW group (WW 54 ± 6% vs. MV surgery 47 ± 5%). Mitral regurgitant volume was significantly lower in the WW group,

TABLE 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
Hemoglobin (g/L)	140 ± 9	143 ± 10	0.45
6MWT distance (m)	406 ± 79	356 ± 76	0.09
Mitral regurgitation etiology			
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 (%). 6MWT = six-minute walk test; 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; MV = mitral valve; MVP = mitral valve prolapse; NYHA = New York Heart Association; TIA = transient ischemic attack; TV = tricuspid valve.

TABLE 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
PMRI 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
Mitral regurgitation volume (mL)	44 ± 12	70 ± 28	**<0.001**	64 ± 20	76 ± 35	0.30
Mitral regurgitation volume index (mL/m^2)	25 ± 7	37 ± 13	**<0.001**	35 ± 12	39 ± 14	0.39
Mitral regurgitation fraction (%)	34 (29–46)	52 (41–58)	**<0.001**	48 ± 10	55 ± 10	0.09
4DF-MR 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
Mitral regurgitation volume (mL)	63 ± 26	83 ± 41	**0.048**	83 ± 34	83 ± 49	0.98
Mitral regurgitation volume index (mL/m^2)	35 ± 15	44 ± 21	0.09	45 ± 20	43 ± 24	0.84
Mitral regurgitation 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 fraction by Teicholz method (%)	63 ± 8	59 ± 9	0.13	60 ± 9	57 ± 8	0.51
Mitral regurgitation volume—PISA (mL)	67 (47–85)	80 (68–112)	**0.04**	103 ± 44	78 ± 30	0.08
Mitral regurgitation volume index (mL/m^2)	32 (24–52)	44 (36–55)	0.14	47 (41–73)	41 (34–48)	0.13
Mitral regurgitation 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

Note: Bolded values represents $P < 0.05$ statistically significant.
Data are presented as mean ± SD and median (IQR1–IQR3). 2D = two-dimensional; 4D = four-dimensional; EROA = effective regurgitant orifice area; LV = left ventricle; MR = cardiac magnetic resonance imaging; MV = mitral valve; PISA = proximal isovelocity surface area; RV = right ventricle; TTE = transthoracic echocardiography; WW = watchful waiting.

than in the MV surgery group (WW 44 ± 12 mL vs. MV surgery 70 ± 28 mL), as was the indexed mitral regurgitant volume and the mitral regurgitant fraction.

With regard to the 4DF-MR parameters, the median aortic stroke volume was significantly higher in the WW group (WW 75 mL [61–82] vs. 56 mL [44–69]). Similar to

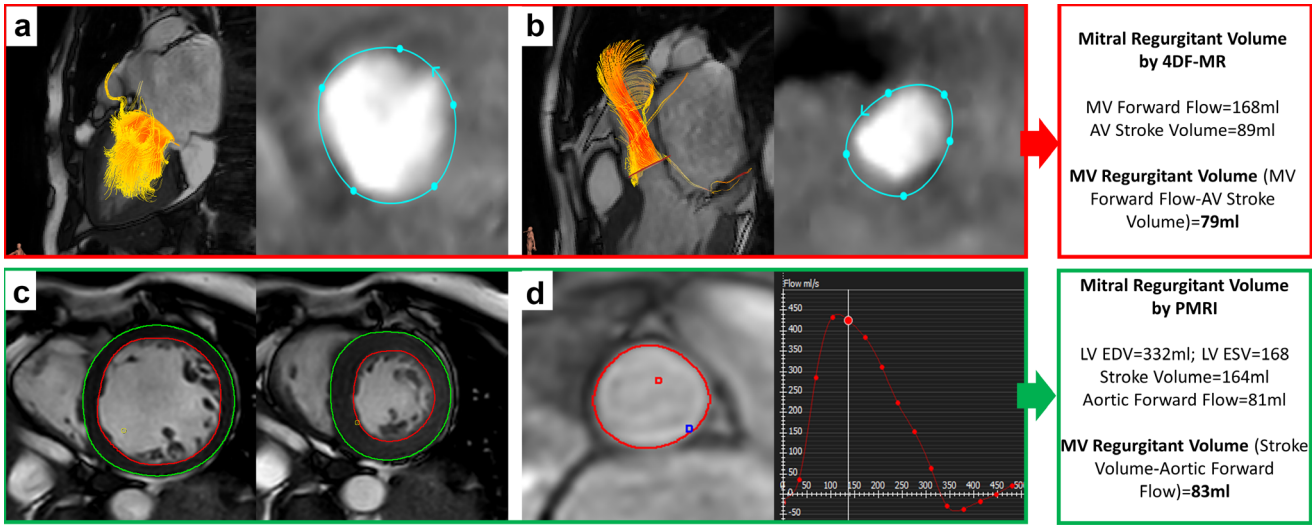

FIGURE 2: An example of assessment of mitral regurgitation by 4DF-MR and PMRI. An example of assessment of mitral regurgitation by the different modalities. Top row presents assessment by 4DF-MR. Panel (a) shows forward flow through the mitral valve and its quantification. Panel (b) shows aortic valve forward flow and its quantification. Middle row presents assessment by PMRI. 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-MR = 4-dimensional flow magnetic resonance imaging; AV = aortic valve; LV EDV = left ventricular end-diastolic volume; LV ESV = left-ventricular end-systolic volume; MV = mitral valve; PMRI = phase-contrast magnetic resonance imaging.

the PMRI findings, mitral regurgitant volume and regurgitant fraction were significantly lower in the WW group (volume WW 58 ± 24 mL vs. MV surgery 79 ± 40 mL and fraction 45 [35–55]% vs. 57 [45–61]%, respectively).

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

MV REPAIR VS. MV REPLACEMENT. When assessed by PMRI, there were no significant differences between the left ventricular (LV end-diastolic volume index MVr 129 ± 35 mL/m^2 vs. 133 ± 34 mL/m^2; $P = 0.50$ and LV ejection fraction 57 ± 8% vs. 52.7%, respectively; $P = 0.12$), right ventricular (RV ejection fraction 48 ± 6% vs. 45 ± 5%, respectively; $P = 0.11$) or mitral regurgitant volume parameters (MVr 62 ± 20 mL vs. MVR 76 ± 35 mL; $P = 0.30$) between these groups.

When assessed by 4DF-MR, mitral regurgitant volume (MVr 79 ± 34 mL vs. MVR 79 ± 47 mL; $P = 0.98$), indexed volume (MVr = 40 [22–57]mL/m^2 vs. MVR 39 ± 14 mL/m^2; $P = 0.89$) and fraction (MVr 56 [38–61]% vs. MVR 59 [45–61]%; $P = 0.78$) were similar between the repair and the replacement group.

With regards to the TTE characteristics, there were also no significant differences between the two groups, Mitral regurgitant volume (MVr 103 ± 44 mL vs. MVR 78 ± 30 mL; $P = 0.08$).

ALL PATIENTS. The relationship between mitral regurgitant volume between the different modalities is demonstrated by Bland–Altman analysis in Fig. 3. The bias was similar between all the modalities: 4DF-MR and PMRI (15; 95% confidence interval [7, 23]), 4DF-MR and TTE (−8; 95% confidence interval [−23, 7]), and PMRI and TTE (−23; 95% confidence interval [−39, −10]). The limits of agreement, however, were narrower between 4DF-MR and PMRI (−35 mL to 65 mL), than between 4DF-MR and TTE (−106 mL to 90 mL), and between PMRI and TTE (−105 mL to 59 mL).

Left and Right Ventricular Reverse Remodeling at 6-Month Follow-Up

"WATCHFUL WAITING" VS. MV SURGERY. There were significant differences in the extent of reverse remodeling at 6-month follow-up between the WW group and patients who underwent MV surgery (Table 4). Compared with WW group, patients in the MV surgery group had a significant reduction in LV end-diastolic volume (WW −2 ± 25 mL vs. MV surgery −61 ± 44 mL), LV stroke volume (WW 1 ± 18 mL vs. MV surgery −55 ± 30 mL), and LV ejection fraction (WW 1 ± 4% vs. MV surgery −11 ± 10%). Left ventricular mass also significantly reduced in the MV surgery group (WW 2 ± 8 g vs. MV surgery −9 ± 18 g). 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 ± 11 mL vs. MV surgery −20 ± 31 mL).

MV REPAIR VS. MV REPLACEMENT. There were no significant differences in the amount of left and right ventricular reverse remodeling at 6 months between patients who underwent MVr and MVR (LV end-diastolic volume MVr -51 ± 33 mL vs. MVR -74 ± 54 mL; $P = 0.18$ and right ventricular end-diastolic volume -21 [-37 to -9]mL vs. -10 [-35 to 7]mL, respectively; $P = 0.32$) (Table 4).

ASSOCIATION OF PRE-OPERATIVE MITRAL REGURGITATION VOLUME AND POST-OPERATIVE LV REVERSE REMODELING. 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 Fig. 4. There was a significant association between the post-operative reduction in the LV end-diastolic volume index and the pre-operative mitral regurgitant volume, when the mitral regurgitant volume was quantified by 4DF-MR and by PMRI. There was no correlation when the mitral regurgitant volume was quantified by the TTE ($P = 0.73$). Furthermore, the receiver operator characteristic curves of mitral regurgitant volume for post-operative reduction in LV end-diastolic volume index (more than mean volume of 32 mL/m^2) demonstrated better performance by 4DF-MR (area under the curve 0.83) and PMRI (area under the curve 0.78), than by TTE (area under the curve 0.51; $P = 0.89$) (Fig. 5).

Clinical Outcomes and Functional Capacity

"WATCHFUL WAITING" VS. MV SURGERY. The mean duration of follow-up was similar in both groups (WW 42.1 $\pm$ 24.9 months vs. MV surgery 51.5 $\pm$ 13.5 months; $P = 0.19$) (Table 5). There were no significant differences between the rate of MACE (WW 5 [33]% vs. MV surgery 8 [27.6]%; $P = 0.74$) between these groups. There was, however, a significant improvement in the 6MWT distance in the MV surgery group (WW 4 $\pm$ 48 m vs. MV surgery 55 $\pm$ 60 m). There was, however, no association between the post-operative LVEDVi change and 6MWT distance change ($P = 0.80$).

MV REPAIR VS. MV REPLACEMENT. There were no significant differences in the rate of the MACE between the MVr and the MVR groups (MVr 5 [31.3]% vs. MVR 3 [23.1]%; $P = 0.70$).

Discussion

We have shown that not only the mitral regurgitant volume quantified by 4DF-MR is in close agreement with PMRI in primary mitral regurgitation, but also, that there is an association between the pre-operative 4DF-MR-derived mitral regurgitant volume and the post-operative reduction in the LV end-diastolic volume index. Furthermore, 4DF-MR demonstrated better performance than PMRI and TTE for identifying a greater than the mean reduction in post-operative LV end-diastolic volume index. Finally, this study has shown no difference in the degree of post-operative left ventricular reverse remodeling or the functional capacity and clinical outcomes between mitral valve repair and replacement.

Quantification of Mitral Regurgitation Volume by 4DF-MR, PMRI, and TTE

Quantification of mitral regurgitation by TTE may be particularly difficult in primary mitral regurgitation, which is frequently complicated by late-systolic, multiple or eccentric jets, rendering the PISA method somewhat inaccurate.[21] Although PMRI overcomes these limitations, 4DF-MR has several advantages, making it potentially a very useful addition to the standard PMRI 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.[27]

Prior studies demonstrated, that 4DF-MR is feasible and reproducible in mitral regurgitation.[28] Moreover, quantification of mitral valve flow by 4DF-MR was accurate even in the presence of atrial fibrillation and regardless of the scanner type and scan protocol.[13,29] A study by Fidock et al showed that mitral regurgitation volume quantitated with 4DF-MR utilizing the indirect method, where 4DF-MR-derived aortic stroke volume was subtracted from 4DF-MR-derived mitral forward flow, was comparable to the standard PMRI assessment; this method also had the highest reproducibility.[12] With regard to TTE, the results were somewhat variable, possibly owing to the different etiologies of mitral regurgitation being evaluated. A recent study of patients with mitral valve prolapse found that TTE assessment yielded much larger regurgitant volumes than PMRI or 4DF-MR, while regurgitant volumes were underestimated by TTE in functional mitral regurgitation.[30,31] In this study, the limits of agreement were narrower between mitral regurgitant volume assessed by 4DF-MR and PMRI, than between 4DF-MR and TTE or PMRI 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 Mitral regurgitant volume, as the PISA radius is obtained from a single systolic frame, which may not accurately reflect the overall severity of mitral regurgitation. The presence of eccentric and multiple regurgitant jets can also render it inaccurate.[21] This may explain the results of this study.

Correlation of Pre-Operative Mitral Regurgitation Volume With Post-Operative LV Reverse Remodeling

The discordance in mitral regurgitation severity between PMRI and TTE has been shown in several studies.[7,8,32] Furthermore, studies showed that mitral regurgitant volume

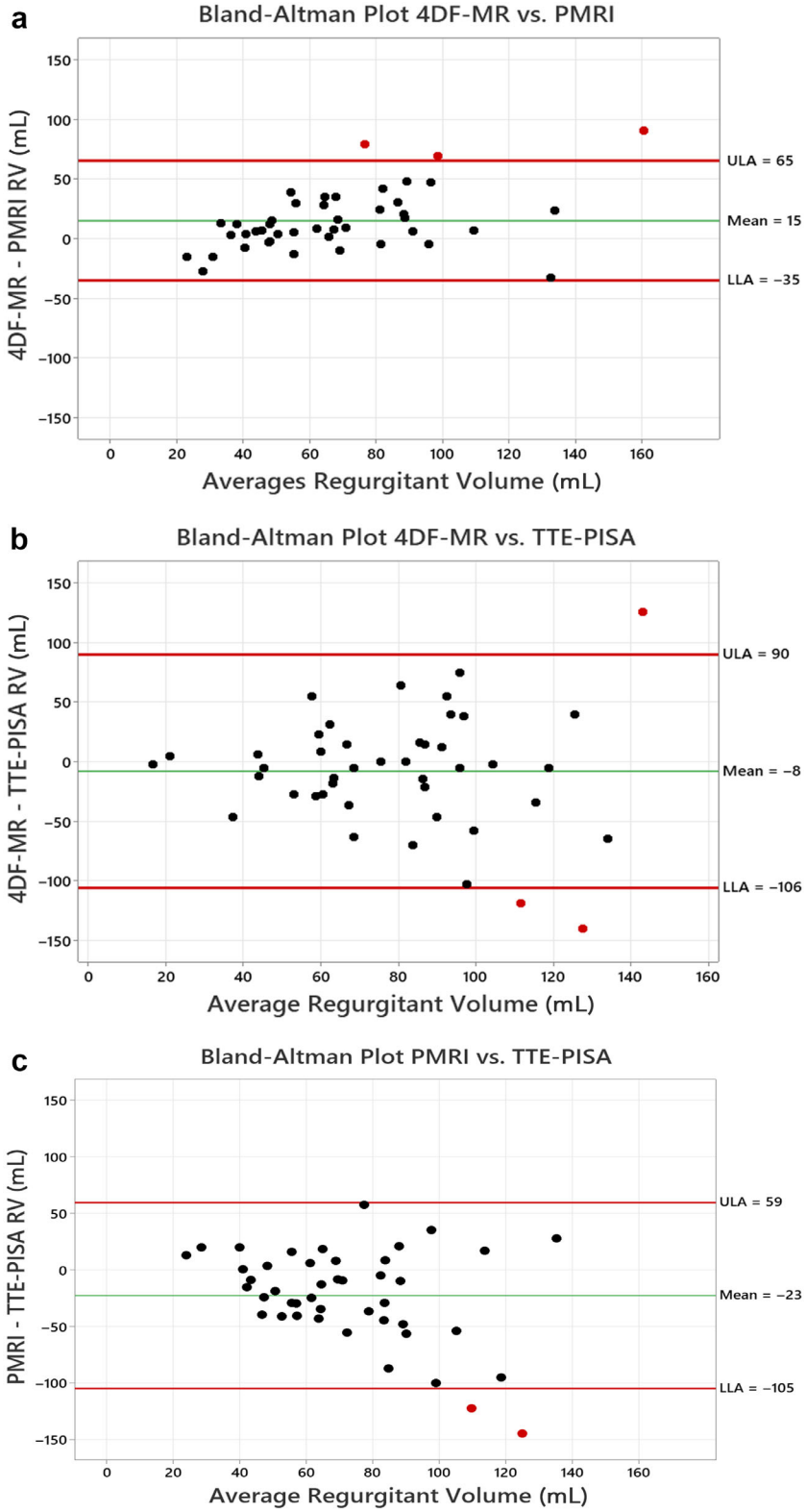

FIGURE 3: Bland–Altman plots. Bland–Altman plots of the relationship between mitral regurgitant volume quantified by: panel (a) 4DF-MR and PMRI, panel (b) 4DF-MR and TTE-PISA and panel (c) PMRI and TTE-PISA. Green line represents bias, which was similar between all modalities: 4DF-MR and PMRI (15), than between 4DF-MR and TTE-PISA (−8) and PMRI and TTE-PISA (−23). The limits of agreement, however, are narrower between 4DF-MR and PMRI, than between the other modalities. 4DF-MR = 4D flow magnetic resonance imaging; LLA = lower limit of agreement; PMRI = phase-contrast magnetic resonance imaging; RV = regurgitant volume; TTE-PISA = transthoracic echocardiography-proximal isovelocity surface area method; ULA = upper limit of agreement.

TABLE 4. Left and Right Ventricular Reverse Remodeling at 6 Months by Cardiac MRI

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 to −9)	−10 (−35 to 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 to −1)	−1 (−9 to 15)	0.054
RV ejection fraction (%)	0 ± 4	1 ± 8	0.33	0 (−4 to 5)	−3 (0–8)	0.08

Note: Bolded values represents $P < 0.05$ statistically significant.
Data are presented as mean ± SD and median (IQR1–IQR3). MR = magnetic resonance imaging; LV = left ventricle; MV = mitral valve; RV = right ventricle.

assessed by PMRI had prognostic associations, while mitral regurgitant volume assessed by TTE did not.[7,8,21] In asymptomatic patients, severe mitral regurgitation by PMRI was the best predictor of progression to surgery and all-cause mortality, whereas in the surgical cohort, there was a significant correlation between the PMRI-assessed mitral regurgitation severity with the post-operative reduction in the left ventricular end-diastolic volume.[7,8,32] Up to date, no studies have examined the relationship between 4DF-MR-derived mitral regurgitant volume and the post-operative LV reverse remodeling. In this study, there was a significant association between the mitral regurgitant volume assessed by 4DF-MR and PMRI with the post-operative reduction in the left ventricular end-diastolic volume index. In line with the aforementioned studies, however there was no correlation between the TTE-derived mitral regurgitant volume and the post-operative decrease in the LV end-diastolic volume index. This holds promise for the clinical applicability of 4DF-MR in the assessment of primary mitral regurgitation.

Furthermore, the receiver operating characteristic analysis in this study showed that, both 4DF-MR- and PMRI-derived mitral regurgitant volume demonstrated superior diagnostic performance to TTE for identification of a more than mean reduction in the post-operative LV end-diastolic volume index. Although no prior studies examined the diagnostic performance of 4DF-MR-derived mitral regurgitant volume in terms of post-operative LV reverse remodeling or clinical outcomes, the previous PMRI studies demonstrated good diagnostic performance of PMRI-derived mitral regurgitant volume for the development of a surgical indication and for all-cause mortality, while TTE showed much lower prognostic value.[7,21]

As both, PMRI and 4DF-MR-derived mitral regurgitant volume in this study was obtained indirectly, errors due to multiple, eccentric and late-systolic jets, which are inherent in primary mitral regurgitation were potentially reduced. Although these indirect methods, which quantitate mitral regurgitant volume by subtracting the aortic forward flow from the LV stroke volume in PMRI and aortic stroke volume from the mitral forward flow in 4DF-MR are also bound by their own limitations, the indirect approach is the preferred PMRI method and the most reproducible 4DF-MR method.[12,17] In summary, this study demonstrates the potential clinical utility of 4DF-MR in assessment of primary mitral regurgitation, which can be either, an add on to a standard PMRI scan protocol to ensure consistency of results or an isolated approach in those unable to

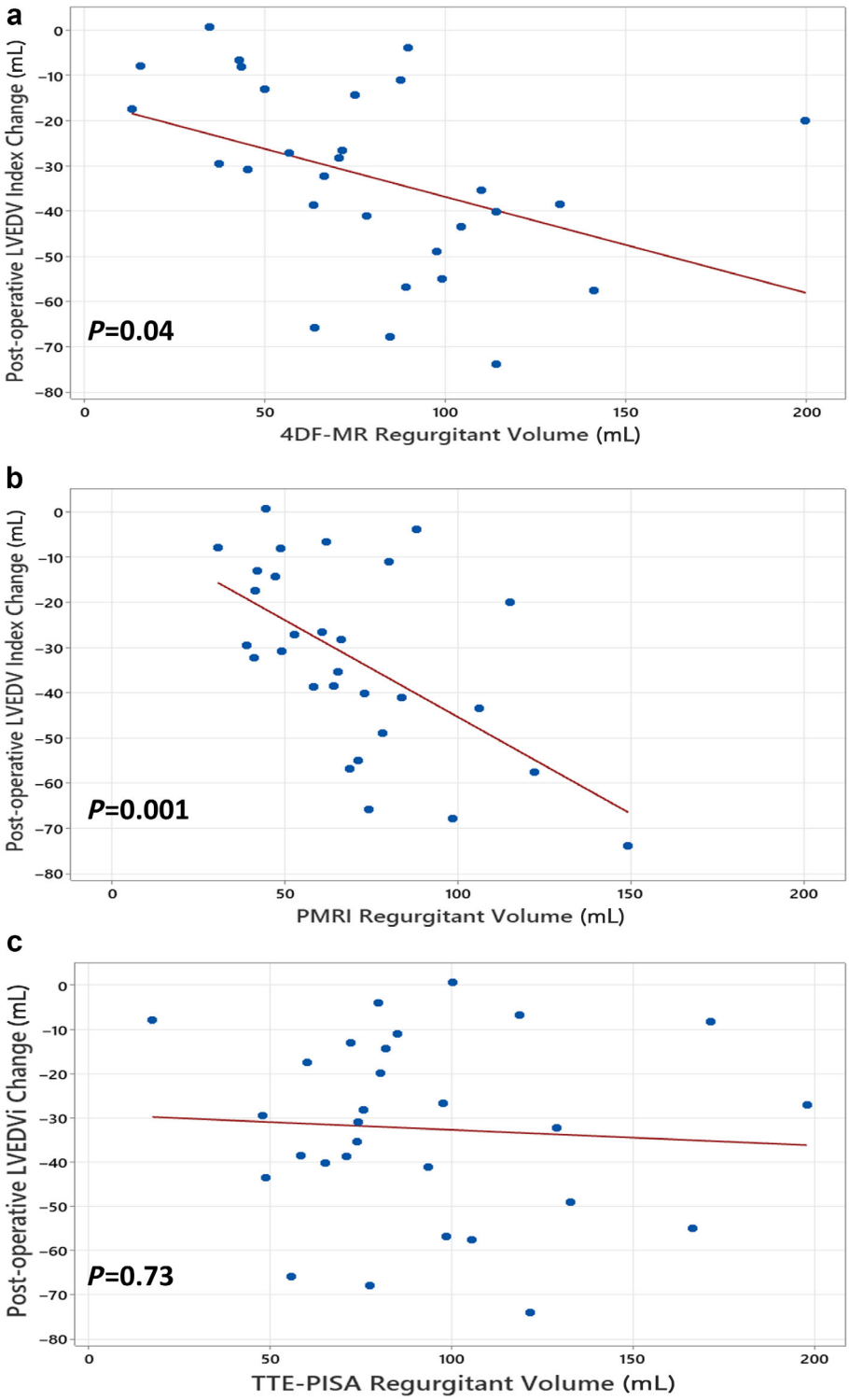

FIGURE 4: Linear regression analysis between post-operative change in LV end-diastolic volume index and pre-operative MR-Rvol. Panel (a) presents mitral regurgitant volume quantified by 4DF-MR, panel (b) by PMRI and panel (c) by the TTE-PISA method. 4DF-MR = 4D flow magnetic resonance imaging; LV = left ventricle; LVEDVi = left ventricular end-diastolic volume index; MR-Rvol = mitral regurgitant volume; PMRI = phase-contrast magnetic resonance imaging; TTE-PISA = transthoracic echocardiography-proximal isovelocity surface area method.

tolerate breath-holding or a full, standard PMRI scan protocol. This study also indicated that TTE-derived mitral regurgitant volume may need to be interpreted with caution in the setting of primary mitral regurgitation.

Left Ventricular Reverse Remodeling 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

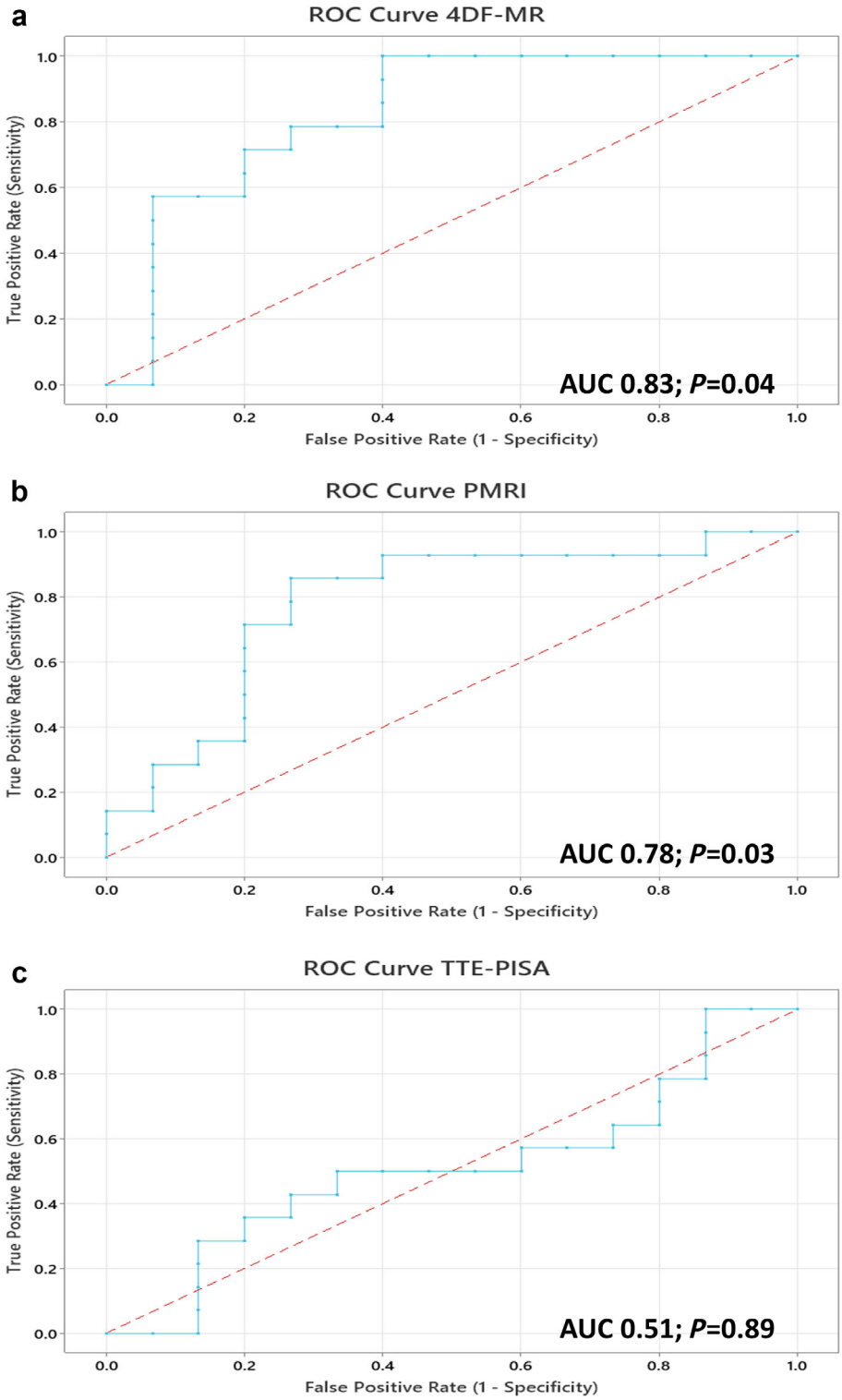

FIGURE 5: Receiver operating characteristic curves. ROC curves of mitral regurgitant volume for reduction of the left ventricular end-diastolic volume index (>mean of 32 mL/m^2). In panel (a), mitral regurgitant volume was quantified by 4DF-MR, in panel (b) by PMRI and in panel (c) by TTE-PISA. The area under the curve is greater with 4DF-MR (0.83; $P = 0.04$) and PMRI (0.78; $P = 0.03$), than with TTE (0.51; $P = 0.89$). 4DF-MR = 4D flow magnetic resonance imaging; PMRI = phase-contrast magnetic resonance imaging; ROC = receiver operating characteristic; TTE-PISA = transthoracic echocardiography-proximal isovelocity surface area method.

durable.[3,4] There are, however no randomized controlled trials to support this approach. While observational studies in primary mitral regurgitation suggest survival advantage in mitral valve repair, the advancement of surgical techniques with the widespread use of chordal preservation techniques may improve the LV reverse remodeling following MVR.[14–16] In this study, there were no significant differences in left and right ventricular reverse remodeling at 6-month

TABLE 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
Hospitalization 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 6-minute walk test distance at 6 months	4 ± 48	55 ± 60	**0.004**	38 ± 47	76 ± 69	0.11

Note: Bolded values represents $P < 0.05$ statistically significant.
Data are presented as mean ± SD and N (%). HF = heart failure; MACE = Major Adverse Cardiovascular Events; MV = mitral valve; TIA = transient ischemic attack; WW = watchful waiting; 6-minute walk test = 6-minute walking test.

follow-up. 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 ± 13.5 months, 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 this study was relatively short, the long-term differences in the rate of MACE remain to be determined.

Limitations

This was a single-center, single-magnet/field strength and single-vendor prospective observational study and thus bound by limitations inherent in all observational studies. This study recruited a small number of only stable patients undergoing elective surgery, who were able to undergo paired study assessments, therefore creating survivor bias. In terms of the echocardiographic evaluation, this study only utilized the TTE-PISA method, which is known to particularly problematic in primary mitral regurgitation.[21] Although this was a relatively small study, prior 4DF-MR studies were similar in size. A large proportion of patients were unfortunately excluded not only due to death and patient's choice, but also due to suboptimal 4DF-MR image quality and artifact as well as lack of a full 4DF-MR dataset availability in some cases. Despite the above limitations, this study does add to the growing body of evidence that 4DF-MR might be useful in assessment of primary mitral regurgitation in contemporary clinical practice.

Conclusions

This study evaluated the relationship between the pre-operative mitral regurgitant volume quantitated by 4DF-MR and the post-operative LV reverse remodeling. Limits of agreement were much narrower between 4DF-MR and PMRI, than between the other modalities. Similar to PMRI, there was a significant correlation between the pre-operative 4DF-MR-derived mitral regurgitant volume in primary mitral regurgitation and the post-operative reduction in the LV end-diastolic volume index, while there was no correlation when the mitral regurgitant volume was assessed by TTE. Moreover, 4DF-MR and PMRI demonstrated superior diagnostic performance to TTE. Although the results need to be verified in a larger study, they hold promise for the clinical utility of 4DF-MR in the future assessment of primary mitral regurgitation.

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References

1. Dziadzko V, Clavel M-A, Dziadzko M, et al. Outcome and undertreatment of mitral regurgitation: A community cohort study. Lancet 2018;391(10124):960-969.
2. Bonow RO, O'Gara PT, Adams DH, et al. 2020 Focused update of the 2017 ACC expert consensus decision pathway on the management of mitral regurgitation: A report of the American College of Cardiology

Solution Set Oversight Committee. J Am Coll Cardiol 2020;75(17): 2236-2270.

3. Baumgartner H, Falk V, Bax JJ, et al. 2017 ESC/EACTS guidelines for the management of valvular heart disease. Eur Heart J 2017;38(36): 2739-2791.
4. Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: A report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation 2021; 143(5):e72-e227.
5. Gajjar K, Kashyap K, Badlani J, Williams RB, Biederman RWW. A review of the pivotal role of cardiac MRI in mitral valve regurgitation. Echocardiography 2021;38(1):128-141.
6. Myerson SG. CMR in evaluating valvular heart disease: Diagnosis, severity, and outcomes. Cardiovasc Imaging 2021;14(10):2020-2032.
7. Penicka M, Vecera J, Mirica DC, Kotrc M, Kockova R, Van Camp G. Prognostic implications of magnetic resonance-derived quantification in asymptomatic patients with organic mitral regurgitation: Comparison with doppler echocardiography-derived integrative approach. Circulation 2018;137(13):1349-1360.
8. Uretsky S, Gillam L, Lang R, et al. Discordance between echocardiography and MRI in the assessment of mitral regurgitation severity: A prospective multicenter trial. J Am Coll Cardiol 2015;65(11):1078-1088.
9. Dyverfeldt P, Bissell M, Barker AJ, et al. 4D flow cardiovascular magnetic resonance consensus statement. J Cardiovasc Magn Reson 2015; 17:72.
10. Blanken CPS, Farag ES, Boekholdt SM, et al. Advanced cardiac MRI techniques for evaluation of left-sided valvular heart disease. J Magn Reson Imaging 2018;48(2):318-329.
11. Feneis JF, Kyubwa E, Atianzar K, et al. 4D flow MRI quantification of mitral and tricuspid regurgitation: Reproducibility and consistency relative to conventional MRI. J Magn Reson Imaging 2018;48(4):1147-1158.
12. Fidock B, Archer G, Barker N, et al. Standard and emerging CMR methods for mitral regurgitation quantification. Int J Cardiol 2021;331: 316-321.
13. Mills MT, Grafton-Clarke C, Williams G, et al. Feasibility and validation of trans-valvular flow derived by four-dimensional flow cardiovascular magnetic resonance imaging in patients with atrial fibrillation. Wellcome Open Res 2021;6:73.
14. Suri RM, Schaff HV, Dearani JA, et al. Survival advantage and improved durability of mitral repair for leaflet prolapse subsets in the current era. Ann Thorac Surg 2006;82(3):819-826.
15. Lazam S, Vanoverschelde JL, Tribouilloy C, et al. Twenty-year outcome after mitral repair versus replacement for severe degenerative mitral regurgitation: Analysis of a large, prospective, multicenter, international registry. Circulation 2017;135(5):410-422.
16. Senechal M, MacHaalany J, Bertrand OF, et al. Predictors of left ventricular remodeling after surgical repair or replacement for pure severe mitral regurgitation caused by leaflet prolapse. Am J Cardiol 2013; 112(4):567-573.
17. Zoghbi WA, Adams D, Bonow RO, et al. Recommendations for noninvasive evaluation of native valvular regurgitation: A report from the American Society of Echocardiography Developed in Collaboration with the Society for Cardiovascular Magnetic Resonance. J Am Soc Echocardiogr 2017;30(4):303-371.
18. Garg P, Swift AJ, Zhong L, et al. Assessment of mitral valve regurgitation by cardiovascular magnetic resonance imaging. Nat Rev Cardiol 2020;17(5):298-312.
19. Suinesiaputra A, Bluemke DA, Cowan BR, et al. Quantification of LV function and mass by cardiovascular magnetic resonance: Multi-center variability and consensus contours. J Cardiovasc Magn Reson 2015; 17(1):63.
20. Schulz-Menger J, Bluemke DA, Bremerich J, et al. Standardized image interpretation and post-processing in cardiovascular magnetic resonance - 2020 update: Society for Cardiovascular Magnetic Resonance (SCMR): Board of Trustees Task Force on Standardized Post-Processing. J Cardiovasc Magn Reson 2020;22(1):19.
21. Myerson SG, d'Arcy J, Christiansen JP, et al. Determination of clinical outcome in mitral regurgitation with cardiovascular magnetic resonance quantification. Circulation 2016;133(23):2287-2296.
22. Garg P, Westenberg JJM, van den Boogaard PJ, et al. Comparison of fast acquisition strategies in whole-heart four-dimensional flow cardiac MR: Two-center, 1.5 Tesla, phantom and in vivo validation study. J Magn Reson Imaging 2018;47(1):272-281.
23. Kamphuis VP, Roest AAW, Ajmone Marsan N, et al. Automated cardiac valve tracking for flow quantification with four-dimensional flow MRI. Radiology 2019;290(1):70-78.
24. Robinson S, Rana B, Oxborough D, et al. A guide for performing adult TTE: The British Society of Echocardiography minimum dataset. Echo Res Pract 2020;7(4):G59-G93.
25. Lambert AS. Proximal isovelocity surface area should be routinely measured in evaluating mitral regurgitation: A core review. Anesth Analg 2007;105(4):940-943.
26. Society AT. ATS statement: The six-minute walk test. Am J Respir Crit Care Med 2002;166(1):111-117.
27. Gorecka M, Bissell MM, Higgins DM, Garg P, Plein S, Greenwood JP. Rationale and clinical applications of 4D flow cardiovascular magnetic resonance in assessment of valvular heart disease: A comprehensive review. J Cardiovasc Magn Reson 2022;24(1):49.
28. Fidock B, Barker N, Balasubramanian N, et al. A systematic review of 4D-flow MRI derived mitral regurgitation quantification methods. Front Cardiovasc Med 2019;6:103.
29. Juffermans JF, Minderhoud SC, Wittgren J, et al. Multicenter consistency assessment of valvular flow quantification with automated valve tracking in 4D flow CMR. JACC: Cardiovasc Imaging 2021;14(7):1354-1366.
30. Spampinato RA, Jahnke C, Crelier G, et al. Quantification of regurgitation in mitral valve prolapse with four-dimensional flow cardiovascular magnetic resonance. J Cardiovasc Magn Reson 2021;23(1):87.
31. Marsan NA, Westenberg JJ, Ypenburg C, et al. Quantification of functional mitral regurgitation by real-time 3D echocardiography: Comparison with 3D velocity-encoded cardiac magnetic resonance. JACC Cardiovasc Imaging 2009;2(11):1245-1252.
32. Uretsky S, Animashaun IB, Sakul S, et al. American Society of Echocardiography algorithm for degenerative mitral regurgitation: Comparison with CMR. JACC Cardiovasc Imaging 2022;15(5):747-760.