Extent and determinants of left ventricular reverse remodeling in patients with secondary mitral regurgitation undergoing MitraClip implantation

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ABSTRACT

Background: In secondary MR, data on left ventricular (LV) remodeling after MitraClip procedure are rare, even this information may impact patient selection. This study investigated changes in LV structure and function by cardiovascular magnetic resonance (CMR) following MitraClip implantation for secondary mitral regurgitation (MR) in order to assess extent and predictors of LV reverse remodeling (LVRR).
Methods and Results: Twenty-nine patients underwent CMR imaging prior to and six months after MitraClip procedure. LVRR was defined by a decrease of LV end-diastolic volume index (LVEDVi) > 15% compared to baseline. According to the definition of LVRR, 34% of patients displayed LVRR at follow-up CMR. Baseline LV stroke volume index (LVSVi), LV ejection fraction (LVEF), LV circumferential strain and MR volume at baseline were predictors of LVRR at follow-up. At second CMR, we detected an improvement in hemodynamic status as illustrated by an increase in effective LVSVi (28 ± 8 ml/m^2 vs. 33 ± 8 ml/m^2; p = 0.053) and cardiac index (2.0 ± 0.5 vs. 2.3 ± 0.5 l/min; p = 0.016), while LVEF and LV strain parameters did not change (p > 0.05). Improvements in effective LVSVi were associated with the decrease of MR volume (r = 0.509; p = 0.018) and MR fraction (r = 0.629; p = 0.002) by MitraClip.
Conclusions: Together, MitraClip implantation is associated with LVRR in one third of patients. Baseline LV function and magnitude of MR are important predictors of LVRR. Improvement of hemodynamic status may be assessed by effective stroke volume index and correlates with the reduction of MR by MitraClip implantation, rather than an increase in LV contractility.

1. Introduction

Transcatheter mitral valve repair (TMVR) with the MitraClip device has evolved to an established treatment option for patients with clinically relevant mitral regurgitation (MR) and elevated surgical risk. While immediate procedural success rates reached 90% and the majority of patients clinically benefits from TMVR, long-term mortality remains substantial and appears to be related to prognosis of underlying heart failure (HF) [1,2,3].

The effect of TMVR on left ventricular (LV) remodeling is highly variable [4]. Previous echocardiographic studies reported LV reverse remodeling (LVRR) in a fraction of about 50% of patients undergoing TMVR with the MitraClip device in various patient cohorts [5,6,7,8]. However, especially in patients with secondary MR, clinical benefit as well as ventricular response following TMVR are less clear. In addition, data on predictors of LVRR after TMVR and its impact on clinical outcome are still limited, though this information may impact patient selection for MitraClip. So far, only few, small studies with mixed cohorts implemented serial cardiovascular magnetic resonance (CMR) scans in patients referred for MitraClip [9,10].

Here, we evaluated the impact of MitraClip implantation on ventricular volumes and function assessed by sequential CMR imaging in order to determine extent and predictors of LVRR in secondary MR.

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Abbreviations

AUC	Area Under the Curve	LVEF	Left Ventricular Ejection Fraction
CAD	Coronary Artery Disease	LVRR	Left Ventricular Reverse Remodeling
CMR	Cardiovascular Magnetic Resonance	LVSVi	Left Ventricular Stroke Volume Index
Effective LVSVi	Effective Left Ventricular Stroke Volume Index	MR	Mitral Regurgitation
HF	Heart Failure	ROC	Receiver Operating Curve
LGE	Late Gadolinium Enhancement	RV	Right Ventricle
LV	Left Ventricle	TMVR	Transcatheter Mitral Valve Repair
LVEDVi	Left Ventricular End-diastolic Volume index	TR	Tricuspid Regurgitation

2. Materials and Methods

Forty patients that underwent MitraClip implantation at the university hospital Duesseldorf, Germany were screened between 2014 and 2018. In eight patients CMR imaging was not possible (claustrophobia n = 3; refused CMR scan n = 3; obesity n = 2). Thus, 32 patients were scheduled for CMR imaging prior to and six months after the procedure. Three patients died prior second CMR scan and were excluded, so that the final patient́s cohort consisted out of 29 patients that all underwent serial CMR scans prior and after TMVR. Patients that were included had severe secondary MR and were considered at high surgical risk by an interdisciplinary heart team. Logistic EuroScore was used for risk stratification. All patients underwent comprehensive cardiological assessment including coronary angiography, right heart catheterization, transthoracic and transesophageal echocardiography prior to the procedure. The study was approved by the ethics committee of the Heinrich-Heine University Duesseldorf (study number 6110R) and executed in accordance with the Declaration of Helsinki. Patients were stratified into two groups according to the presence of LVRR. LVRR was defined as previously described by a decrease of LV end-diastolic volume index (LVEDVi) > 15% at second CMR compared to baseline [6,11].

CMR was conducted with a 1.5 Tesla MRI scanner (Achieva, Philips Medical Systems, Best, The Netherlands) using a 32-channel phased array coil. Functional and structural assessment was determined by cine steady state free precession (SSFP) images in standard long axis geometries (two-, three- and four-chamber view) as well as in short axis orientation. Flow and velocities in the ascending aorta and pulmonary trunk were determined by using through plane velocity encoded imaging in a retrospective gating technique during one single breath hold. LV and right ventricular (RV) volumes were assessed by manually tracing endocardial borders at end-diastole and end-systole in each of the short-axis cine images. In case of atrial fibrillation, three beats were averaged. LV and RV end-diastolic volume and end-systolic volume were assessed using the slice summation method and matched to body surface area to calculate LV and RV end-systolic and end-diastolic volume indices (LVESVi/RVESVi/LVEDVi/RVEDVi). The LV and RV stroke volume index (LVSVi/RVSVi) was the difference between LVEDVi and LVESVi as well as RVEDVi and RVESVi. Effective LVSV reflecting the LV forward flow into the aorta was calculated by the difference of total aortic forward flow minus aortic backward flow and indexed to body surface area (effective LVSVi). In 27 patients, gadolinium-based contrast agent (ProHance®, Bracco Imaging) was given for assessment of late gadolinium enhancement (LGE). Two patients did not receive contrast agent due to reduced renal function. Post processing analyses were performed offline using commercial software (cmr42, Circle Cardiovascular Imaging Inc., Calgary, Alberta, Canada and Extended Workspace, Philips Healthcare, Hamburg, Germany). Strain analysis was accomplished using dedicated software (Image-Arena Version 3.0 and 2D Cardiac Performance Analysis MR Version 1.1.0; TomTec Imaging Systems Unterschleissheim, Germany).

Patients were scheduled for a second CMR scan six months after the MitraClip procedure. All-cause mortality, HF-hospitalizations and New York Heart Association (NYHA) class III/IV were assessed during 12 months follow-up. The clinical course was monitored by follow-up examinations, phone calls to the referring cardiologists and the patients' primary physicians or the patients themselves.

2.1. Statistical analysis

All analyses were performed using SigmaPlot (Systat Sotware Inc., San Jose, California, USA) and Graphpad Prism (Graphpad Software, San Diego, USA). Data for continuous variables are presented as mean ± SD or median with interquartile range. Continuous variables were tested by the Kolmogorov-Smirnov test to assess normality of distribution. Categorical variables are presented as frequencies and proportions. Differences between two groups were compared for significance with a two-tailed unpaired t-test. Fisheŕs exact test was used to examine the significance of the association between two kinds of classification. Simple logistic regression analysis was performed to assess predictors of LVRR at follow-up. Multivariate analysis was not performed due to low number of events. Receiver operating curve (ROC) analysis was constructed to evaluate strongest predictors of LVRR and Youdeńs Index for optimal thresholds. Correlation between the change of MR volume and MR fraction and the change in effective LVSVi was assessed by Pearson correlation. For all analyses, a p-value of < 0.05 was considered to be statistically significant.

3. Results

The final patient cohort included 29 patients that underwent CMR imaging prior and 5 ± 2 months following MitraClip implantation. Baseline patient characteristics are shown in Table 1. The medication of the patient cohort during the study period is given in Table S1 and Figure S1. Mean age was 77 ± 7 years, 58% were female and 18 patients (62%) had atrial fibrillation. At baseline, median NT-proBNP was 2440 (1273–3542) ng/l. Etiology of mitral valve disease was classified secondary in 25 patients (85%) and mixed in four patients (15%). According to Carpentieŕs classification, 15 patients (52%) were assigned to Carpentier class I and 14 patients (48%) to Carpentier class IIIb. Mean LVEF was 44 ± 13% (Table 2).

One third of patients (34%) displayed LVRR (decrease of LVEDVi > 15%) at follow-up CMR, while the remaining patients (66%) did not (Fig. 1). Table 2 compares baseline CMR parameters of LVRR and Non-LVRR patients. In logistic regression analysis, baseline LVSVi, LVEF, LV circumferential strain and MR volume at baseline were predictors of LVRR at follow-up (Table 3). ROC

Table 1
Baseline Patient Characteristics.

Baseline Data	Overall N = 29	Non-LVRR N = 19	LVRR N = 10	p-Value
Clinical characteristics				
Age (years)	77 ± 7	77 ± 6	77 ± 9	0.862
BMI (kg/m^2)	25 ± 6	24 ± 7	26 ± 4	0.496
Women, N (%)	14 (48)	10 (53)	4 (40)	0.699
Hypertension, N (%)	25 (86)	15 (79)	10 (100)	0.268
Diabetes mellitus, N (%)	4 (14)	2 (11)	2 (20)	0.592
Vascular disease, N (%)	3 (10)	2 (11)	1 (10)	0.999
Coronary artery disease, N (%)	23 (79)	15 (79)	8 (80)	0.999
Previous CABG, N (%)	11 (38)	7 (37)	4 (40)	0.999
Previous VS, N (%)	4 (14)	3 (16)	1 (10)	0.999
Atrial fibrillation, N (%)	18 (62)	13 (68)	5 (50)	0.432
Logistic EuroSCORE (%)	27 ± 15	28 ± 14	26 ± 16	0.505
NYHA III/IV, N (%)	21 (72)	12 (63)	9 (90)	0.201
Labratory assessment				
Serum Creatinine (mg/dl)	1.4 ± 0.5	1.3 ± 0.4	1.5 ± 0.8	0.353
Estimated GFR (ml/min/m^2)	49 ± 17	49 ± 13	49 ± 23	0.959
Hemoglobine (mg/dl)	12 ± 2	12 ± 2	12 ± 2	0.555
NT-proBNP (pg/ml)	2440 (1273–3542)	2711 (1388–4408)	2238 (978–3241)	0.346

Abbreviations: LVRR = Left ventricular reverse remodeling; BMI = Body mass index; CABG = Coronary artery bypass grafting; VS = Valve surgery; NYHA = New York Heart Classification; GFR = Glomerular filtration rate; NT-proBNP = NT-pro-Brain natriuretic peptide.

Table 2
Baseline CMR parameters according to the presence of left ventricular reverse remodeling.

CMR at Baseline	Overall N = 29	Non-LVRR N = 19	LVRR N = 10	p-Value
LVEDVi (ml/m^2)	103 ± 33	105 ± 37	99 ± 25	0.651
LVESVi (ml/m^2)	60 ± 31	68 ± 34	46 ± 18	0.071
LVSVi (ml/m^2)	43 ± 11	38 ± 6	54 ± 12	**<0.001**
LVEF (%)	44 ± 13	39 ± 12	52 ± 10	**0.002**
Effective LVSVi (ml/m^2)	28 ± 8	25 ± 7	32 ± 8	0.082
Cardiac Index (L/min/m^2)	2.0 ± 0.5	1.8 ± 0.5	2.2 ± 0.5	0.060
MR Vol (ml)	28 ± 17	26 ± 18	32 ± 16	**0.038**
MR Fraction (%)	33 ± 16	33 ± 18	32 ± 11	0.651
RVEDVi (ml/m^2)	79 ± 19	76 ± 19	84 ± 19	0.386
RVESVi (ml/m^2)	41 ± 13	42 ± 16	40 ± 8	0.714
RVSVi (ml/m^2)	36 ± 12	34 ± 11	41 ± 12	0.147
RVEF (%)	46 ± 11	45 ± 12	48 ± 11	0.557
TR Vol (ml)	16 ± 15	15 ± 15	19 ± 18	0.661
TR Fraction (%)	19 ± 18	19 ± 19	20 ± 16	0.864
GLS (%)	−15 ± 6	−13 ± 5	−18 ± 7	**0.046**
Circumferential Strain (%)	−22 ± 12	−18 ± 8	−30 ± 13	**0.013**
Radial Strain (%)	29 ± 17	24 ± 13	37 ± 20	0.071
Presence of LGE, N (%)	13 (48)	10 (53)	3 (30)	0.433

Abbreviations: LVRR = Left ventricular reverse remodeling; LVEDVi = Left ventricular end-diastolic volume index; LVESVi = Left ventricular end-systolic volume index; LVSVi = Left ventricular stroke volume index; LVEF = Left ventricular ejection fraction; MR Vol = Mitral regurgitation volume; RVEDVi = Right ventricular end-diastolic volume index; RVESVi = Right ventricular end-systolic volume index; RVSVi = Right ventricular stroke volume index; RVEF = Right ventricular ejection fraction; TR Vol = Tricuspid regurgitation volume; GLS = Global longitudinal strain; LGE = Late gadolinium enhancement.

analysis indicated that LVRR at follow-up was best predicted by baseline LVSVi > 45 ml/m^2 (AUC 0.900; 95% CI (0.732–1.000), LVEF > 40% (AUC 0.834; 95% CI (0.693–0.981), LV circumferential strain < -24% (AUC 0.778; 95% CI (0.561–0.995) and MR volume > 27 ml (AUC 0.765; 95% CI 0.544–0.977).

One third of patients (30%) with LVRR had evidence of LGE at baseline CMR, while every second patient (53%) in the non-LVRR group showed LGE at initial CMR (p = 0.433)(Table 2). When stratifying patients according to the presence of coronary artery disease (CAD), in the LVRR group all patients with evidence of LGE had CAD, while in the non-LVRR cohort 80% of patients with evidence of LGE had CAD.

In the entire population, MitraClip implantation effectively decreased MR volume from 28 ± 17 ml to 9 ± 17 ml (p < 0.001). Similarly, MR fraction was reduced from 33 ± 16% to 10 ± 19% (p < 0.001). Mean mitral valve gradient after TMVR as assessed by echocardiography was 3.3 ± 1.1 mmHg. At follow-up CMR, we detected a decrease of LVSVi (Fig. 2). LVEDVi decreased numerically without reaching statistical significance. There were no changes in LVESVi and LVEF (Fig. 2). Furthermore, we detected a

trend towards improved effective LVSVi (LV forward flow) (Fig. 2). In line with this, there was an increase in cardiac index at comparable heart rates (73 ± 16 beats/min vs. 74 ± 15 beats/minute; p = 0.813)(Fig. 2). Increased effective LVSVi (LV forward flow) following MitraClip implantation correlated with the decrease of MR volume and MR fraction through TMVR (Fig. 3). LV strain analysis demonstrated no changes of LV global longitudinal strain (-15 ± 6% vs. −14 ± 7%; p = 0.548), circumferential strain (−22 ± 11% vs. −20 ± 9%; p = 0.550) and radial strain (29 ± 17% vs. 27 ± 12%; p = 0.701) after MitraClip implantation.

By definition, patients with LVRR were characterized by reduced LVEDVi and LVSVi (Table 4). LVESVi, LVEF and LV strain parameters did not change at follow-up examination (Table 4). Moreover, effective LVSVi (LV forward flow) and cardiac index increase numerically without reaching statistical significance at follow-up in LVRR patients (Table 4). Also, in patients without LVRR, MitraClip implantation reduced MR severity (Table 4). As expected, there were no changes of LV volumes and function in this group (Table 4). Furthermore, effective LVSVi (LV forward flow) and cardiac index tended to improve in this group either (Table 4).
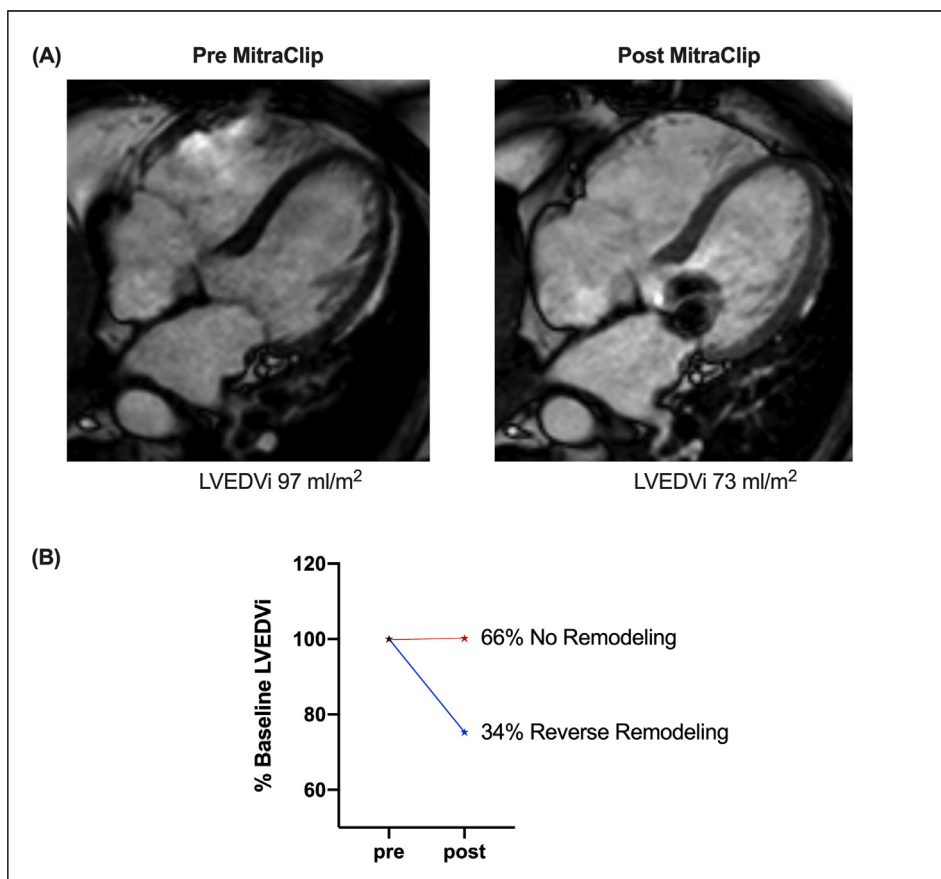
Fig. 1. (A) CMR images of a patient prior to and post MitraClip implantation. End-diastolic images in a four-chamber view prior to and six months after MitraClip procedure. Post procedure the MitraClip causes a dark distinction artefact. (B) According to the definition of left ventricular reverse remodeling (LVRR) (defined by a decrease of LVEDVi > 15%), one third of patients (34%) experienced LVRR, while the remaining two thirds (66%) did not. Abbreviations: LVEDVi = Left ventricular end-diastolic volume index; LVRR = Left ventricular reverse remodeling.

Table 3
Prediction of left ventricular reverse remodeling at follow-up by pre-interventional CMR.

Predictors of LVRR Reverse Remodeling at Follow-up			
Baseline CMR Parameters	OR	95% CI	P-Value
LVESVi (per ml/m^2 increase)	0.971	0.933 to 1.000	0.088
LVSVi (per ml/m^2 increase)	1.244	1.095 to 1.540	**0.008**
LVEF (per % increase)	1.152	1.051 to 1.314	**0.010**
Effective LVSVi (per ml/m^2 increase)	1.123	0.995 to 1.310	0.086
Cardiac Index (per l/min/m^2)	1.002	1.000 to 1.005	0.083
Global Longitudinal Strain (per % increase)	0.856	0.708 to 0.993	0.063
Circumferential Strain (per % increase)	0.892	0.789 to 0.976	**0.031**
Radial Strain (per % increase)	1.054	0.998 to 1.113	0.091
MR Volume (per ml increase)	1.099	1.022 to 1.212	**0.027**

Abbreviations: LVRR = Left ventricular reverse remodeling; LVEDVi = Left ventricular end-diastolic volume index; LVESVi = Left ventricular end-systolic volume index; LVSVi = Left ventricular stroke volume index; LVEF = Left ventricular ejection fraction; MR Vol = Mitral regurgitation volume; RVEDVi = Right ventricular end-diastolic volume index; RVESVi = Right ventricular end-systolic volume index; RVSVi = Right ventricular stroke volume index; RVEF = Right ventricular ejection fraction; TR Vol = Tricuspid regurgitation volume; GLS = Global longitudinal strain; LGE = Late gadolinium enhancement.

In any group, we did not detect any reduction in RV volumes nor an improvement of RV function following MitraClip (Table 4).

During 18 ± 7 months follow-up, 17% of patients died, additional 13% experienced HF-hospitalizations. Seventeen per cent of patients presented with persistent dyspnea according to NYHA class III/IV at follow-up. There were no differences in clinical outcome in patients with and without LVRR at follow-up (Table 5).

4. Discussion

The present study investigated changes of ventricular volumes and myocardial function after MitraClip implantation with serial CMR in order to assess determinants of LVRR and their relationship with clinical outcome. The main findings are: 1) One third of patients undergoing MitraClip implantation in our cohort experienced LVRR as defined by a marked reduction of LVEDVi indicating diastolic LV unloading; 2) LVRR at follow-up was associated with baseline LV function and the magnitude of MR at baseline; 3) MitraClip implantation led to an improvement in hemodynamic status illustrated by an increase in effective LVSVi (LV forward flow) and cardiac index. In this regard, stroke volume index better represents improvements in hemodynamic status, rather than ejection fraction or strain parameters; and 4) The increase in effective LVSVi following TMVR was correlated with the decrease of MR volume and MR fraction through MitraClip implantation.

According to the definition of LVRR (decrease of LVEDVi > 15%), in our study one third of patients revealed LVRR. This is a little bit less compared to previous studies that demonstrated LVRR in about 50% of patients undergoing MitraClip procedure, while the definition of LVRR slightly varies [6,7,8]. Average decrease of LVEDVi in our cohort was −10 ± 8 ml/m^2 which is quite similar with the decrease of LVEDV in patients with secondary MR in the EVERST trial and somewhat less compared to previous studies
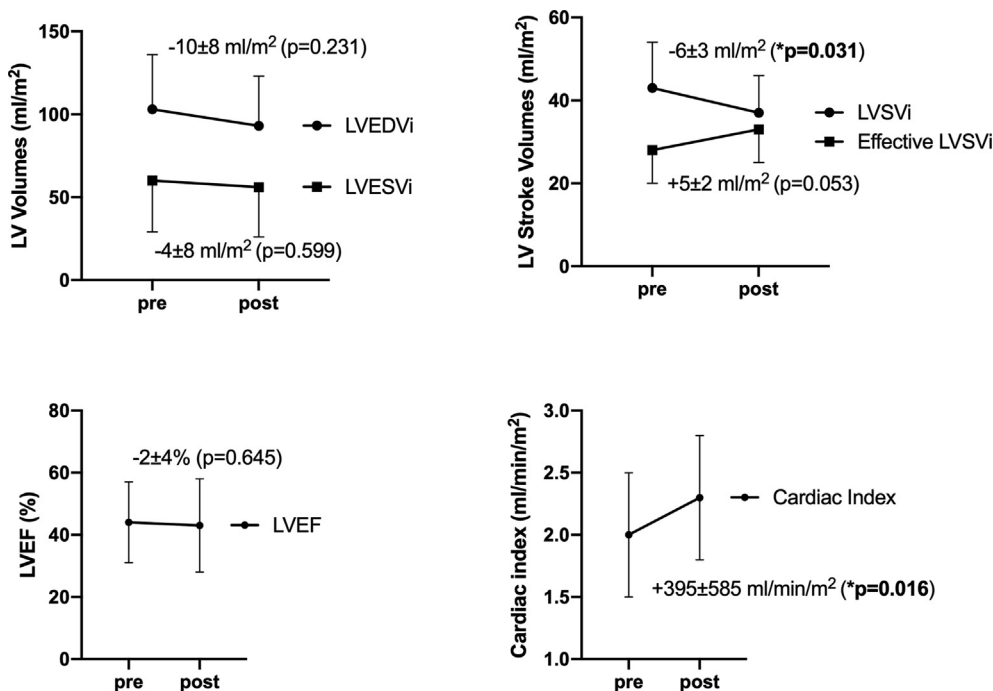
Fig. 2. Left ventricular volumes and function prior to and 6 months after MitraClip implantation. Abbreviations: LVEDVi = Left ventricular end-diastolic volume index; LVESVi = Left ventricular end-systolic volume index; LVSVi = Left ventricular stroke volume index; effective LVSVi = Effective left ventricular stroke volume index (=LV forward flow); LVEF = Left ventricular ejection fraction.
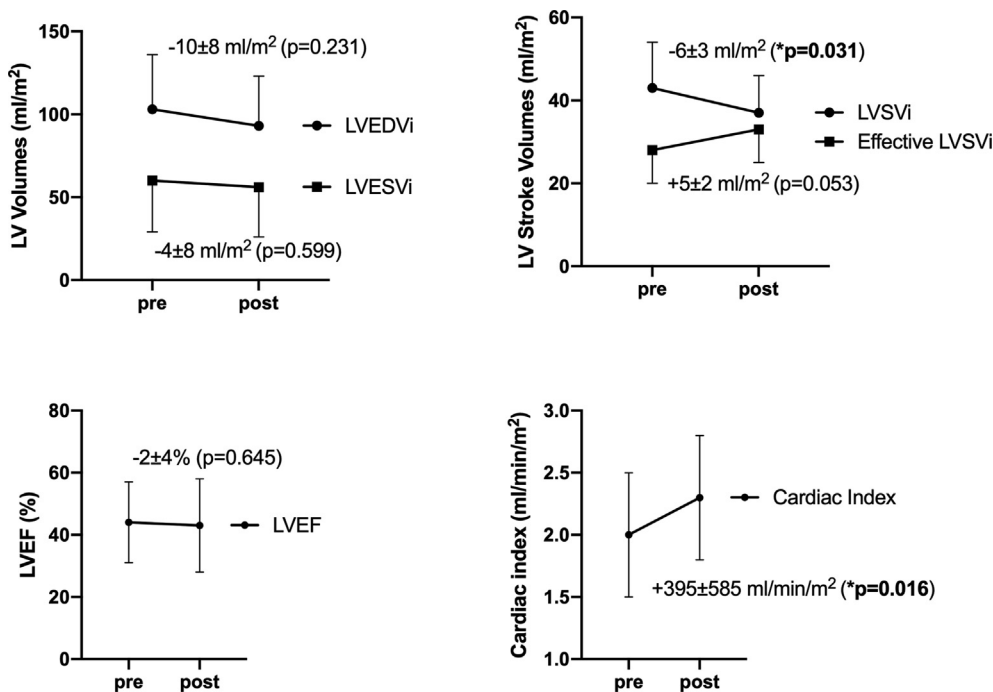
[6,8,12,13,14]. Predictors of LVRR were baseline LV function and the magnitude of MR at baseline. Regarding LV function, larger LVSVi, increased LVEF and LV circumferential strain at baseline were associated with LVRR. This is an important finding in patients with secondary MR that might suffer from a potentially irreversible underlying LV pathophysiology (e.g. ischemic cardiomyopathy). In this regard, baseline LVSVi (<45 ml/m^2), LVEF (<40%) and LV circumferential strain (<−23%) seem to be capable in identifying sub-

jects that will not experience LV unloading through TMVR or, on the other hand, those patients in whom the increase in afterload counterbalanced the reduction in LV preload [15]. As shown in previous studies, afterload mismatch is associated with lower LVEF and may lead to adverse clinical outcomes [16,17]. Thus, indication for TMVR needs to be set with caution and further treatment options (e.g. LV assist device implantation) should be discussed early in these patients. Moreover, larger MR volume at baseline

Table 4
CMR parameters at baseline and at follow-up in patients with left ventricular reverse remodeling (LVRR) and without (Non-LVRR).

CMR Parameter	Non-LVRR N = 19			LVRR N = 10		
	Baseline	Follow-up	p-Value	Baseline	Follow-up	p-Value
LVEDVi (ml/m^2)	105 ± 37	103 ± 30	0.831	99 ± 25	74 ± 19	**0.024**
LVESVi (ml/m^2)	68 ± 34	67 ± 30	0.989	46 ± 18	35 ± 15	0.165
LVSVi (ml/m^2)	38 ± 6	36 ± 9	0.479	54 ± 12	40 ± 10	**0.010**
LVEF (%)	39 ± 12	37 ± 12	0.619	52 ± 10	54 ± 13	0.982
Effective LVSVi (ml/m^2)	25 ± 7	30 ± 7	0.143	32 ± 8	38 ± 8	0.101
Cardiac Index (L/min/m^2)	1.8 ± 0.5	2.1 ± 0.4	**0.047**	2.2 ± 0.5	2.7 ± 0.8	0.068
MR Vol (ml)	26 ± 18	8 ± 16	**<0.001**	32 ± 16	9 ± 12	**0.003**
MR Fraction (%)	33 ± 18	12 ± 23	**<0.001**	32 ± 11	13 ± 19	**0.009**
RVEDVi (ml/m^2)	76 ± 19	78 ± 17	0.743	84 ± 19	89 ± 25	0.681
RVESVi (ml/m^2)	42 ± 16	43 ± 12	0.876	40 ± 8	42 ± 17	0.789
RVSVi (ml/m^2)	34 ± 11	35 ± 12	0.777	41 ± 12	47 ± 14	0.442
RVEF (%)	45 ± 12	45 ± 11	0.909	48 ± 11	53 ± 21	0.327
TR Vol (ml)	15 ± 15	9 ± 6	0.795	19 ± 18	18 ± 7	0.951
TR Fraction (%)	19 ± 19	16 ± 11	0.961	20 ± 16	23 ± 19	0.785
Global Longitudinal Strain (%)	−13 ± 5	−13 ± 5	0.840	−18 ± 7	−16 ± 9	0.526
Circumferential Strain (%)	−18 ± 8	−15 ± 6	0.307	−30 ± 13	−29 ± 7	0.843
Radial Strain (%)	24 ± 13	22 ± 8	0.664	37 ± 20	35 ± 15	0.837

Abbreviations see Table 2.

Table 5
One-year clinical outcome in relation to left ventricular remodeling following MitraClip procedure.

	Non-LVRR N = 19	LVRR N = 10	p-Value
All-cause mortality, N (%)	3 (16)	2 (20)	0.775
HF-hospitalization, N (%)	2 (13)	1 (13)	0.999
NYHA class III/IV, N (%)	2 (13)	2 (25)	0.439

Abbreviations: LVRR = Left ventricular reverse remodeling; HF-hospitalization = Heart failure hospitalization; NYHA = New York Heart Association.

was a predictor of LVRR at follow-up. After publication of MITRA-FR and COAPT, we face an ongoing discussion about optimal patient selection for TMVR. In this regard, Grayburn proposed a conceptual framework of "proportionate" and "disproportionate" MR considering magnitude of MR in relation to degree of LV dilatation and function to identify patients that may benefit from TMVR [18]. In the current study, we did not focus on proportionate and disproportionate MR, however, even in our small cohort, MR volume at baseline was larger in the LVRR group compared to the Non-LVRR cohort (Table 2). Thus, the magnitude of MR at baseline seems to be another important factor that is associated with LV remodeling after MitraClip implantation in secondary MR.

However, not only LV function and MR volume, but also pre-existing structural LV alterations are discussed to impact LVRR and may therefore be useful in risk stratification prior mitral valve interventions (e.g. in selecting the appropriate timing for mitral valve surgery in degenerative MR). Van de Heyning et al. included 41 patients with degenerative MR undergoing CMR and showed an association between the presence of LGE and LV remodeling [19]. In our cohort, the presence of LGE was not associated with LVRR at follow-up. Even when stratifying patients to the presence of CAD, there was no association between the presence of LGE and LVRR. Theoretically, patients with potentially irreversible changes of myocardial structure (e.g. ischemic scar tissue) may experience less distinct changes in LV volumes and function. In future trials, T1 Mapping techniques may provide further insights into the impact of myocardial structure on LV remodeling, as T1 Mapping and Extracellular Volume Mapping are more sensitive in detecting not only focal but also diffuse fibrosis with prognostic impact in various patient populations (e.g. in patients with non-ischemic cardiomyopathy) [20].

In the entire cohort, only LVSVi was significantly reduced at follow-up, while there was a slight decrease of LVEDVi (-10 ± 8 ml/

m^2). LVESVi remained unchanged at second CMR. These findings can be elucidated by a reduction of LV volume overload, and a potentially increase in LV afterload as LVESVi did not decrease [15]. However, this remains speculative because we did not directly measure afterload in this study. LV systolic function (LVEF) as well as strain parameters remained unaffected following TMVR. However, and despite the fact that LVSVi was reduced, effective LVSVi (LV forward flow) and cardiac index rose six months after TMVR. Thus, MitraClip implantation led to a significant decrease of MR volume which further reduced LV preload and resulted in improved hemodynamics following the procedure. In this regard, effective stroke volume index better represents hemodynamic improvements than LVEF or strain parameters, as we observed an increase in effective LVSVi (LV forward flow) while LVEF and strain parameters remained unchanged following MitraClip. However, the improvement in hemodynamic status was not associated with presence of LVRR at follow-up. But rather, the reduction of MR volume and MR fraction through MitraClip implantation were associated with improvements in effective LVSVi (LV forward flow) (Fig. 3). Thus, we assume that the improvement in hemodynamic status is mainly achieved through the reduction of regurgitant flow and thereby diastolic LV unloading. The pathophysiological basis of this phenomenon has been demonstrated by Gaemperli et al. who demonstrated an 21% increase in LV afterload and conversely a 17% decrease of LV preload acutely after MitraClip procedure through invasive measurements [15]. Similarly, in their study the improvement in hemodynamic status was not associated with LV contractility. Likewise, in the study of Lurz et al. a reduction of LV preload following MitraClip implantation did not lead to acutely improved LVEF and LV strain parameters at follow-up CMR 7 days after TMVR [9]. These observations are in accordance with several echocardiographic studies that show an increase in LV forward flow while LVEF remained unaffected after TMVR [5,6]. The fact that the increase in effective LVSVi following TMVR was correlated with the decrease of MR volume and MR fraction through MitraClip implantation underlines the importance of procedural success with a sufficient reduction of MR. Grayburn et al. investigated LV remodeling during the first year after MitraClip procedure and found that the correction of volume overload was associated with the degree of residual MR [4]. Moreover, in large registries residual moderate to severe MR was associated with adverse prognosis [21,22]. This together with our findings suggests that a sufficient reduction of MR volume is of utmost importance to achieve hemodynamic improvement, and thus, most clinical benefit for patients.

During one-year follow-up, clinical outcome was similar in patients with and without LVRR. However, we only included a small patient cohort and our study was not powered for outcome analysis. Adamo et al. demonstrated improved clinical outcomes in patients with LVRR in a larger cohort of patients with secondary MR (184 patients) that underwent MitraClip implantation [7]. Similarly, Nita et al. showed in a mixed cohort including 164 patients with primary and secondary MR that LVRR determined by echocardiography was associated with reduced rates of major adverse cardiovascular events two years after MitraClip [23]. Thus, there is evidence for an association between LVRR and improved clinical outcomes.

5. Study limitations

We included a small but distinct patient cohort. Thus, multivariable analysis on predictors of LV remodeling was not performed. However, this is the largest cohort of MitraClip patients published so far, undergoing sequential CMR imaging. We focused on patients with secondary MR only, thus creating a decisive patient population for comprehensive CMR assessment. In this regard, our study population reflects a real-world setting with a typical mixture of inoperable, high- and intermediate risk patients with secondary MR that currently undergo MitraClip implantation. Due to the sample size, cut-off values for prediction of LV remodeling at follow-up cannot be transmitted one-to-one in clinical practice but might be a benchmark.

6. Conclusions

TMVR with the MitraClip device induces LVRR in more than one third of patients. This is accompanied by an improvement in hemodynamic status six months after the procedure, which can be assessed by effective stroke volume index (effective LVSVi), rather than ejection fraction or strain parameters. LV function and magnitude of MR at baseline are predictors of LVRR. The hemodynamic improvement following TMVR is not associated with LVRR at follow-up, but with the reduction of MR through MitraClip implantation. Thus, reduction of regurgitant flow, rather than an increase in LV contractility seems to account for hemodynamic improvement following TMVR.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgment

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2021.100804.

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