Advanced echocardiographic imaging in valvular and systemic diseases

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CHAPTER 4

Implications of Left Ventricular Dimensions prior to Transcatheter Mitral Valve Repair on Left Ventricular Reverse Remodelling and Outcome

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Under revision at Structural Heart

ABSTRACT

Aim: To assess the association between baseline left ventricular (LV) dimensions and the occurrence of LV reverse remodeling (LVRR) at follow-up as well as the combined endpoint of all-cause mortality or cardiovascular hospitalizations after transcatheter mitral valve repair with the MitraClip device.

Methods and Results: A total of 107 patients with symptomatic moderate-to-severe and severe mitral regurgitation (MR) (age 75±9 years, 57% male, 79% functional MR) receiving MitraClip and with complete 6-month echocardiographic follow-up were evaluated. LVRR, defined as a reduction of ≥10% in LV end-diastolic diameter (LVEDD) after 6 months, occurred in 34 (32%) patients. Although baseline characteristics were similar between patients with LVRR and without LVRR, patients without LVRR had larger LVEDD and lower LV ejection fraction at baseline (66±10mm vs. 62±7mm, p=0.037 and 37±13% vs. 44±14%, p=0.026 respectively). On multivariate regression analysis, baseline LVEDD <65mm was independently associated with LVRR (HR 3.665 95%CI: 1.284–10.465, p=0.015). During a median follow-up of 24 months, 41 patients died and 38 patients presented cardiac events (defined as heart failure hospitalizations, repeated transcatheter mitral valve repair, surgical mitral valve replacement and LV assist device implantation). The composite endpoint occurred in 57 (53%) patients. Patients with baseline LVEDD <65mm showed better composite endpoint-free survival compared to patients with LVEDD ≥65 mm. In addition, patients who developed LVRR at 6 months follow-up had a better composite endpoint-free survival than their counterparts during a 3-year follow-up period.

Conclusion: Development of LVRR after treatment with MitraClip device is influenced by the extent of LV dilatation at baseline. Baseline LVEDD <65m was associated with better composite endpoint-free survival and is therefore an important parameter to take in account in the decision making for optimal treatment strategies.

INTRODUCTION

The volume overload imposed by chronic severe mitral regurgitation (MR) leads to hemodynamic and structural remodeling of the left ventricle (LV) and left atrium (LA) [1]. Both surgical and transcatheter mitral valve repair (TMVR) using a MitraClip device induce hemodynamic unloading, reduce myocardial wall stretch and lead to LV reverse remodeling (LVRR) with marked reductions in LV and LA dimensions and improved LV systolic function.[2-4] However, LVRR is not observed in all patients. It has been suggested that the extent of LV dilatation prior to surgical restrictive mitral valve repair has been shown to impact the occurrence of LVRR in patients with secondary MR[4, 5]. A previous study, identified a cut-off value of LV end-diastolic diameter (LVEDD) ≥65 mm to be independently associated with low probability of LVRR after surgical restrictive mitral annuloplasty and with reduced survival in patients with secondary MR.[4, 6] To date, it has not been explored whether these findings can also be observed in patients undergoing TMVR, which may be important for patient selection given the myriad of transcatheter interventions that are being developed. The Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation (MITRA-FR) trial and the Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT) trials have suggested that baseline characteristics in terms of severity of MR and LV dimensions may be important to understand the discrepant results.[7, 8] The aim of the present study was to assess whether baseline LVEDD, especially a previously published cut-off value of LVEDD <65mm[4], is associated with LVRR and long-term event-free survival from all-cause mortality or cardiovascular hospitalisations.

METHODS

A total of 107 consecutive patients with symptomatic, moderate-to-severe or severe MR who underwent TMVR with the MitraClip device (Abbott Vascular, Venlo, CA, USA) and completed 6-month clinical and echocardiographic follow-up were included. Demographic, clinical, echocardiographic and procedural data were prospectively collected in the departmental cardiology information system (EPD-Vision; Leiden University Medical Center, Leiden, The Netherlands) and retrospectively analysed. Changes in clinical symptoms (New York Heart Association [NYHA] functional class, 6-minute walk distance and the quality of

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life according to the Minnesota Living With Heart Failure® questionnaire)[9] and echocardiographic parameters were assessed 6 months after transcatheter mitral valve repair. LVRR was defined as a reduction of ≥10% in LVEDD at 6 months follow-up. Patients were divided according to the occurrence of LVRR and the baseline clinical and echocardiographic characteristics and the procedural results were compared between them. The association between baseline LVEDD and the occurrence of LVRR was investigated taking into consideration clinical, echocardiographic and procedural variables that may influence the association. In addition, the relation between baseline LVEDD and 6-month LVRR and all-cause mortality and cardiac events was evaluated. The institutional ethical committee approved this evaluation and waived the need for patient written informed consent for retrospective analysis of clinically collected data.

Two-dimensional echocardiography data acquisition and analysis

All patients underwent echocardiography in the left lateral decubitus position, using a commercially available system (E9; General Electric-Vingmed, Horten, Norway) and a 3.5 MHz or M5S transducer in the standard parasternal and apical views. M-mode and two-dimensional (2D), colour, pulsed and continuous wave Doppler data were stored in cine-loop format. Offline analysis was performed using commercially available post-processing data software (EchoPAC BT13; GE Medical Systems, Horten, Norway).

Conventional echocardiographic parameters included LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV) and LV ejection fraction (LVEF) measured according to the biplane Simpson's method.[10] Interventricular septum thickness, LVEDD, LV end-systolic diameter (LVESD), posterior wall thickness and LA diameter were measured according to current guidelines.[10] LA volume index (LAVI) was also measured from the apical 4- and 2-chamber views with the biplane Simpson's method.[10] LV diastolic function was assessed according to current recommendations and included peak early (E) and late (A) diastolic velocities and E-wave deceleration time measured on pulsed wave Doppler recordings of the trans-mitral flow.[11] In addition, E' was measured at the lateral and septal mitral annulus with pulsed wave tissue Doppler imaging and the average was calculated. The E/E' ratio was then calculated.[11] The systolic pulmonary arterial pressure (sPAP) was estimated by measuring the tricuspid regurgitation peak velocity on continuous wave Doppler recordings. The right atrial pressure estimated by the inferior vena cava diameter and degree of respiratory collapse were also taken into consideration to estimate the sPAP.[12] Right ventricular function was evaluated by measuring the tricuspid annular plane systolic excursion (TAPSE).[13]

MR severity was graded based on the proximal isovelocity surface area method and assessment of the vena contracta using 2D colour Doppler recordings of the mitral valve.[14] Residual MR at 6 months follow-up was quantified as previously described and graded as none or mild (grade 0-1), to severe (grade 3) and severe (grade 4).[15] The mean transmitral gradient was measured using the continuous wave Doppler method.

Transcatheter mitral valve repair procedure

Transcatheter MitraClip implantation was performed under general anaesthesia and guided with fluoroscopy and transesophageal echocardiography as previously described.[16, 17] When necessary, more than one device was implanted for optimal MR reduction without creating valve stenosis. Successful transcatheter MitraClip implantation was defined as a reduction of MR to grade ≤2.

Follow-up and outcomes

Patients were followed-up at the outpatient clinic. The occurrence of LVRR was assessed at 6 months follow-up. The endpoint of this study was a composite of all-cause mortality or cardiac events (heart failure hospitalisations, transcatheter or surgical re-intervention because of MitraClip failure, LV assist device implantation) occurring after 6 months of follow-up.

Statistical analyses

Data analyses were performed using the SPSS® software version 23.0 (IBM, Armonk, NY, USA). Continuous variables are presented as mean±standard deviation if normally distributed or as median and interquartile range (IQR) if not normally distributed. Normal distribution was tested with the Shapiro-Wilk test. Categorical variables are reported as frequencies and percentages. Comparisons between patients with LVRR versus no-LVRR were performed with the one-way analysis of variance (ANOVA) or the Mann-Whitney U test for continuous variables and with the chi-square test for the categorical variables. Changes in continuous variables over time were compared with linear mixed model analysis with unstructured covariance matrix or Wilcoxon signed-rank test. Baseline parameters associated with LVRR were assessed with univariable and multivariable logistic regression analyses. Survival analysis was performed using the Kaplan-Meier method and the time from 6 months follow-up to the occurrence of all-cause mortality or cardiac events was calculated and compared between groups of patients divided according to baseline LVEDD (<65mm vs ≥65mm) and the occurrence of LVRR at 6 months. A P value <0.05 was considered statistically significant.

RESULTS

Baseline clinical and echocardiographic characteristics for the overall population

Clinical characteristics of the overall population (mean age 75±9years, 57% male) are summarized in Table 1. The majority of patients had secondary MR (79%). The transcatheter MitraClip implantation procedures were successful (achieving MR grade ≤2) in 100 patients (93%), whereas in 7 patients (7%) MR grade remained ≥3 after the procedure. After 6 months follow-up, 34 (32%) patients showed LVRR defined as a reduction of ≥10% of the LVEDD.

Changes in clinical parameters in patients with versus without LVRR

No significant differences in clinical characteristics were observed between patients with and without LVRR (Table 1). During the 6 months of clinical follow-up, patients with LVRR and without LVRR showed similar improvements in NYHA class (Figure 1) and quality of life scores (from score 34 [IQR:21-53] to 27 [IQR:11-43], P=0.030 and 36 [IQR: 24-53] to 29 [IQR: 14-43], P=0.008 respectively). Improvement in 6 minute walk distance was more pronounced in patients with LVRR as compared to patients without LVRR (288±129 to 340±161m, P=0.077 and 309±147 to 323±130m, P=0.950 respectively).

Table 1. Baseline clinical characteristics in the total population and a comparison between patients with versus without left ventricular reverse remodeling.

Clinical variables	Total (n=107)	LVRR (n=34)	No LVRR (n=73)	*P* value
Age years	75 ± 9	74 ± 10	76 ± 8	0.322
Male, n (%)	61 (57)	23 (68)	38 (52)	0.129
BSA	1.9 ± 0.2	1.9 ± 0.2	1.9 ± 0.2	0.878
Sinus rhythm, n (%)	51 (48)	15 (44)	36 (49)	0.616
CRT, n (%)	36 (34)	11 (32)	25 (34)	0.460
Prior myocardial infarction, n (%)	43 (40)	12 (35)	31 (43)	0.481
CABG, n (%)	25 (23)	11 (32)	14 (19)	0.134
Previous PCI, n (%)	42 (39)	13 (38)	29 (40)	0.833
Hypertension, n (%)	50 (47)	12 (35)	38 (52)	0.106
Hypercholesterolemia, n (%)	35 (33)	9 (27)	26 (36)	0.348
Diabetes, n (%)	28 (26)	7 (21)	21 (29)	0.370
(Ex-)Smoker, n (%)	40 (37)	11 (32)	29 (40)	0.463
COPD, n (%)	16 (15)	3 (9)	13 (18)	0.225
NYHA > II, n (%)	71 (66)	21 (62)	50 (69)	0.493
6 minute walk distance,m	302 ± 141	288 ± 129	309 ± 147	0.495
Quality of life	36 (23 – 53)	34 (21 – 53)	36 (24 – 53)	0.608
eGFR, ml/min/1.73m^2	55 ± 25	57 ± 25	54 ± 24	0.518
Log EuroSCORE (%)	14 (7 – 24)	19 (7 – 26)	13 (6 – 21)	0.149
Medications, n (%)				
ACEi/ARB	81 (76)	24 (71)	57 (78)	0.400
Beta-blocker	87 (81)	28 (82)	59 (81)	0.850
Calcium channel blocker	11 (10)	3 (8)	8 (11)	0.735
Statin	66 (62)	22 (65)	44 (60)	0.661
Diuretics	92 (86)	30 (88)	62 (85)	0.647

ACEi; angiotensin converting enzyme inhibitor. ARB; angiotensin II receptor blockers. BSA; body surface area. CABG; coronary artery bypass graft. COPD; chronic obstructive pulmonary disease. CRT; cardiac resynchronization therapy. eGFR; estimated glomerular filtration rate. IQR: interquartile range. NYHA: New York Heart Association. PCI; percutaneous coronary intervention.

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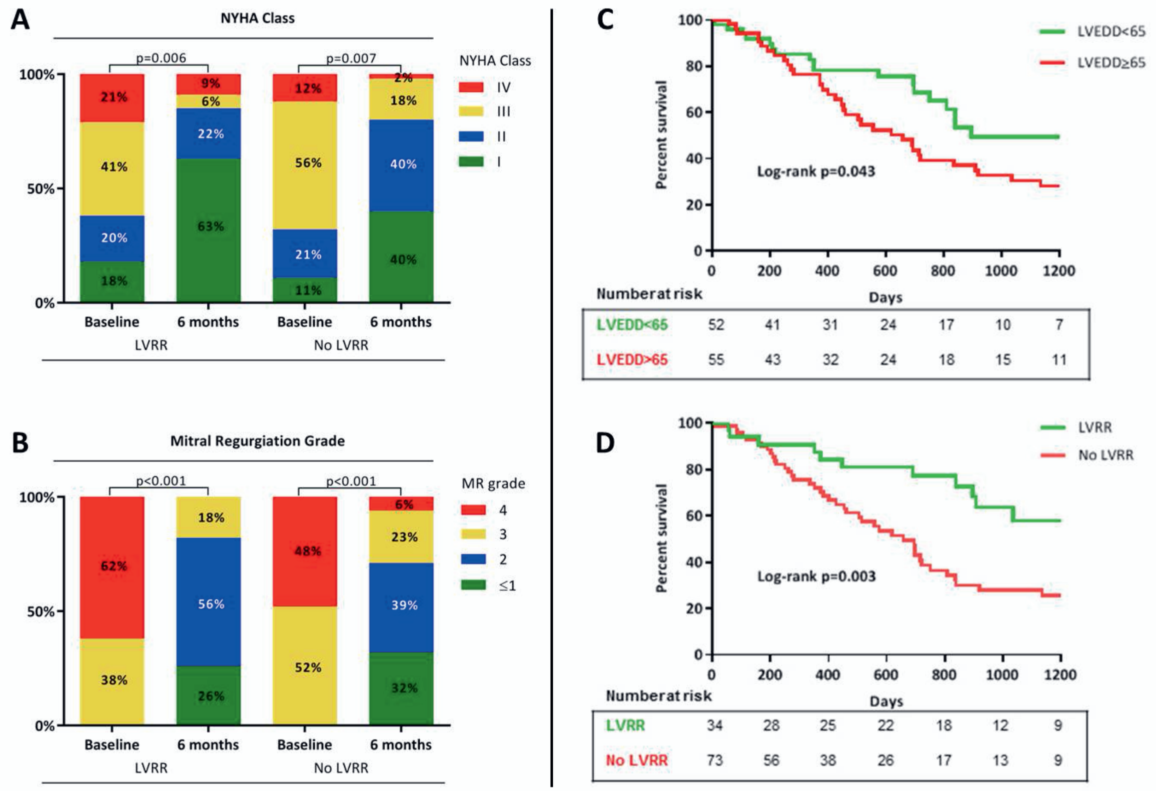

Figure 1. Panel A and B: *Changes in NYHA class (panel A) and mitral regurgitation grade (panel B) in patients with and without left ventricular reverse remodeling (LVRR) after transcatheter mitral valve repair.* ***Panel C and D:*** *Kaplan-Meier curves for time from 6 months follow-up to endpoint (combined all-cause mortality or cardiac events) according to the occurrence of left ventricular end-diastolic diameter (LVEDD; A) by the cut-off value of 65mm (above) and left ventricular reverse remodeling (LVRR; B).*

Changes in echocardiographic parameters between patients with versus without LVRR

The echocardiographic characteristics at baseline for patients with and without LVRR at 6 months follow-up are summarized in Table 2. Although baseline LV volumes were similar in both groups, patients who developed LVRR after 6 months had a significantly better LVEF at baseline compared to patients without LVRR. Additionally, LVEDD was smaller and the number of patients with baseline LVEDD <65mm was significantly higher in patients presenting with LVRR as compared to patients without LVRR. LV diastolic function was significantly better in patients with LVRR. No significant differences were observed in sPAP or TAPSE. In addition, the mitral EROA and regurgitant volume were similar in both groups. Interestingly, compared to patients without LVRR, patients with LVRR had a significantly higher diastolic transmitral valve gradient at baseline.

Table 2. Echocardiographic parameters at baseline in patients with versus without left ventricular reverse remodeling 6 months after transcatheter mitral valve repair

Baseline echocardiographic parameters		LVRR (n=34)	No LVRR (n=73)	*P* value
LVEDV, ml		173 ± 78	170 ± 77	0.873
LVESV, ml		95 (52 – 131)	86 (63 – 162)	0.915
LV ejection fraction, %		44 ± 14	37 ± 13	0.026
IVST, mm		9 (9 – 11)	9 (8 – 11)	0.731
LVEDD, mm		62 ± 7	66 ± 10	0.037
LVEDD >65mm, n (%)		10 (29)	45 (62)	0.002
LVESD, mm		46 ± 12	47 ± 12	0.704
PWT, mm		9 ± 2	10 ± 2	0.433
Left atrial diameter, mm		50 ± 11	51 ± 7	0.687
LAVI, ml		68 ± 30	63 ± 20	0.258
E-wave, cm/s		98 ± 25	97 ± 31	0.921
E’, cm/s		8 ± 3	7 ± 2	0.034
E/E’ ratio		15 ± 6	17 ± 7	0.213
sPAP, mmHg		34 (28 – 51)	41 (32 – 51)	0.323
TAPSE, mm		17 ± 4	17 ± 3	0.741
MR grade, n (%)				0.185
	≤1	0 (0)	0 (0)	
	II	0 (0)	0 (0)	
	III	13 (38)	38 (52)	
	IV	21 (62)	35 (48)	
EROA, cm^2		19 (12 – 29)	20 (13 – 31)	0.566
Regurgitant volume, ml		30 (18 – 44)	32 (22 – 52)	0.442
TMG, mmHg		2.17 ± 0.88	1.80 ± 0.87	0.045

IVST: Interventricular septum thickness. LAVI: left atrial volume index. LV: left ventricular. LVEDd: left ventricular end-diastolic diameter. LVESd: left ventricular end-systolic diameter. LVEDV: left ventricular end-diastolic volume. LVESV: left ventricular end-systolic volume. LVRR: left ventricular reverse remodeling . PWT: posterior wall thickness. sPAP: systolic pulmonary arterial pressure. TAPSE: tricuspid annular plane systolic excursion. TMG: transmitral gradient

Both patient groups showed similar reductions in MR grade after 6 months follow-up (Figure 1) with MR grade ≤2 in 82% of LVRR patients and 71% in no-LVRR patients (P=0.242). During the 6 months follow-up, LVEDV decreased significantly in patients with LVRR whereas in patients without LVRR, LVEDV did not change (Figure 2). The LVESV showed

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similar decrease in both groups of patients while no significant changes were observed in LVEF in either group. Per definition, LVEDD decreased significantly in LVRR patients, whereas patients without LVRR showed a significant increase in LVEDD (Figure 2). Similarly, LVESD decreased not significantly in patients with LVRR whereas in patients without LVRR, LVESD increased. LAVI remained stable in LVRR patients but increased in patients without LVRR (from 68±30 to 69±35ml, P=0.926 and from 63±20 to 66±24ml, P=0.0.041 respectively). Although comparable decrease of E' was observed in both groups of patients with and without LVRR (from 8±3 to 6±2cm/s, P<0.001 and 7±2 to 6±2cm/s, P<0.001 respectively), the increase of E/E' ratio observed in both groups was significantly more prominent in patients without LVRR (from 15±6 to 20±8, P=0.002, and 16±7 to 27±12, P<0.001 respectively, *P*=0.002). The sPAP and TAPSE remained unchanged in both groups. Furthermore, both patient groups showed comparable increases in transmitral gradient at 6 months follow-up (from 2.17±0.88 to 4.37±2.14mmHg, P<0.001, in patients with LVRR and 1.80±0.87 to 3.71±1.67mmHg, P<0.001 in patients without LVRR).

Clinical, echocardiographic and procedural variables associated with LV reverse remodeling at 6 months follow-up

Table 3 provides the univariable correlates of LVRR at 6 months follow-up. Better LVEF, smaller LVEDD (as continuous variable) and LVEDD <65mm, higher E' and higher transmitral gradients were significantly associated with the occurrence of LVRR 6 months after transcatheter MitraClip implantation. Limited by the number of patients with LVRR, two multivariable logistic regressions were performed containing three parameters each (Table 4). In both models, a baseline LVEDD <65 mm was independently associated with the development of LVRR after 6 months.

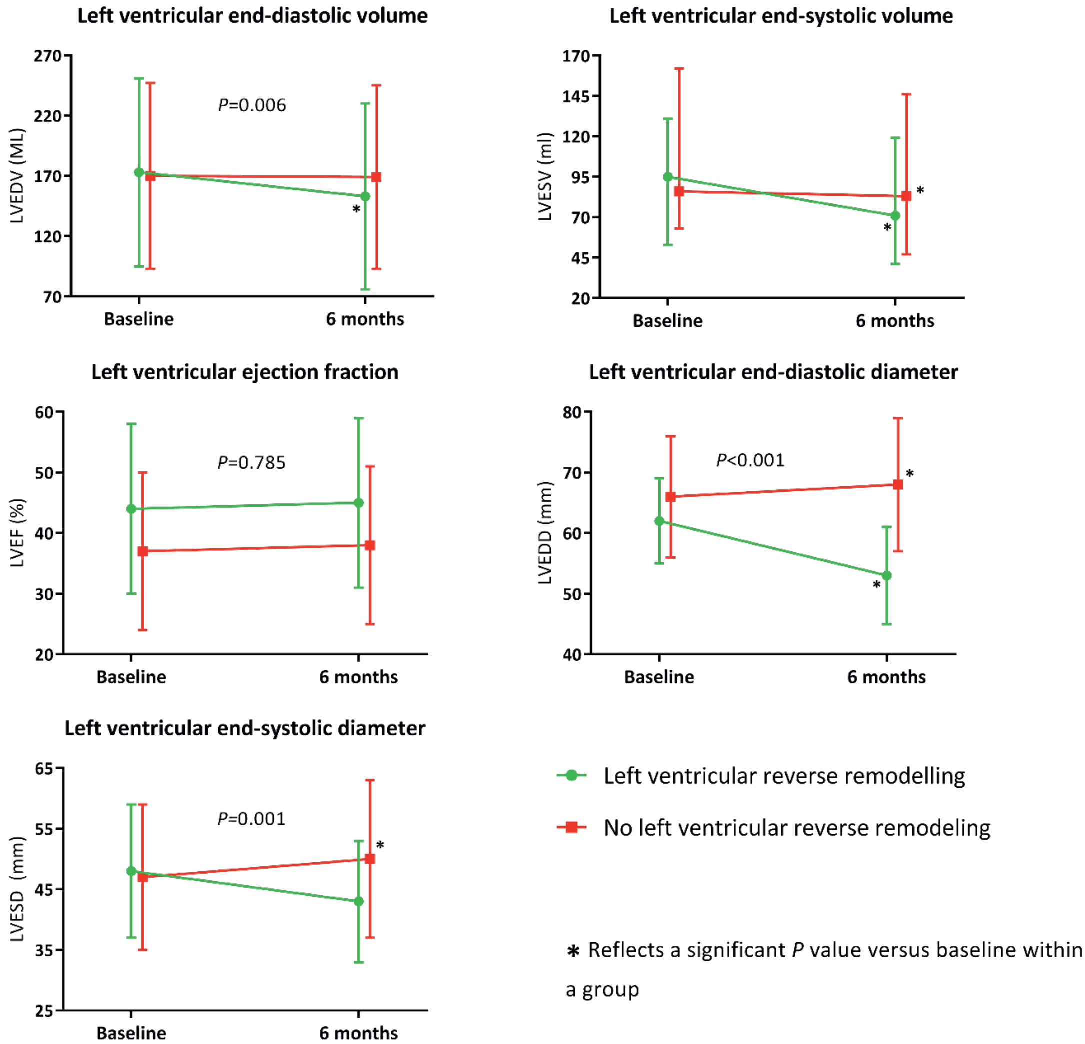

Figure 2. *Comparison of echocardiographic parameters at baseline and 6 months in patients with versus without left ventricular reverse remodeling (LVRR).*

Association between baseline LV dimensions and 6-month LVRR and all-cause mortality and cardiac morbidity

After the 6-month echocardiographic evaluation, 41 patients died and 38 patients presented with cardiac events (31 heart failure hospitalisations, 4 repeated transcatheter mitral valve repair, 2 surgical mitral valve replacement and 1 LV assist device implantation). The composite endpoint occurred in 57 patients.

The Kaplan-Meier curves in Figure 1, panel B, shows that the patients with baseline LVEDD <65 mm had significantly better event-free survival compared to patients with larger LVEDD ≥65 mm (panel A). In addition, patients with LVRR at 6 months follow-up showed better event-free survival as compared to patients without LVRR (panel B).

Table 3. Univariable logistic regression analyses for left ventricular reverse remodeling 6 months after transcatheter mitral valve repair.

	Univariable analyses		
Baseline parameters	OR	95% CI	P value
Age, years	0.977	0.934 – 1.022	0.309
Male	1.926	0.821 – 4.518	0.132
BSA	1.154	0.190 – 7.003	0.876
Sinus rhythm	0.811	0.358 – 1.838	0.616
CRT	0.931	0.376 – 2.306	0.878
Prior myocardial infarction	0.739	0.318 – 1.716	0.482
CABG	2.016	0.799 – 5.083	0.138
Previous PCI	0.939	0.407 – 2.166	0.883
Hypertension	0.502	0.217 – 1.164	0.108
Hypercholesterolemia	0.651	0.265 – 1.601	0.349
Diabetes	0.642	0.242 – 1.700	0.372
(Ex-)Smoker	0.726	0.308 – 1.711	0.464
COPD	0.444	0.115 – 1.715	0.239
NYHA >II	1.346	0.575 – 3.148	0.493
6 minute walk distance, m	0.999	0.996 – 1.002	0.490
Quality of life	0.997	0.978 – 1.016	0.758
eGFR, ml/min/1.73m2	1.006	0.989 – 1.022	0.514
Log EuroSCORE	1.021	0.990 – 1.052	0.188
LVEDV, ml	1.000	0.995 – 1.006	0.871
LVESV, ml	1.000	0.994 – 1.006	0.892
LVEF, %	1.035	1.004 – 1.068	0.029
IVST, mm	0.930	0.759 – 1.141	0.488
LVEDD, mm	0.951	0.906 – 0.998	0.041
LVEDD <65mm	3.857	1.607 – 9.259	0.003
LVESD, mm	0.993	0.958 – 1.029	0.701
PWT, mm	0.921	0.752 – 1.129	0.429
LA diameter, mm	0.990	0.944 – 1.038	0.684
LAVI, ml	1.010	0.993 – 1.027	0.264
E-wave, cm/s	1.001	0.986 – 1.015	0.920
E’, cm/s	1.196	1.010 – 1.414	0.037
E/E’ ratio	0.958	0.896 – 1.025	0.213
sPAP, mmHg	0.985	0.957 – 1.015	0.320
TAPSE, mm	0.980	0.868 – 1.106	0.738
MR grade	1.754	0.765 – 4.023	0.185
EROA, cm^2	0.983	0.945 – 1.022	0.390
Regurgitant volume, ml	0.992	0.966 – 1.019	0.573
TMG, mmHg	1.595	1.001 – 2.542	0.049

For abbreviations see table 1 and 2.

Table 4. Multivariable logistic regression analyses for left ventricular reverse remodeling 6 months after transcatheter mitral valve repair.

Baseline parameters	Multivariable analysis			Multivariable analysis		
	OR	95% CI	P value	OR	95% CI	P value
LVEF, %	1.006	0.964 – 1.049	0.794	1.010	0.973 – 1.048	0.602
LVEDd <65mm	3.665	1.284 – 10.465	0.015	3.300	1.192 – 9.139	0.022
E’, cm/s	1.124	0.909 – 1.390	0.280			
TMG, mmHg				1.501	0.914 – 2.466	0.109

For abbreviations see table 1 and 2.

DISCUSSION

The present study demonstrates that LVRR at 6 months follow-up, defined as LVEDD decrease ≥10%, occurred in 32% of patients after TMVR with the MitraClip device. A baseline LVEDD <65 mm was independently associated with LVRR. Furthermore, patients with a baseline LVEDD <65 mm had better event-free survival at 3 years of follow-up after MitraClip implantation. Patients who experienced LVRR at 6 months follow-up had a better event free survival (all-cause mortality or cardiovascular hospitalisations).

Effects of transcatheter mitral valve repair on LV reverse remodeling

Transcatheter mitral valve repair with MitraClip implantation reduces the regurgitant volume, resulting in hemodynamic LV unloading and subsequent reduction of myocardial wall stretch. These changes would result in parallel reductions of LV dimensions and development of LVRR. The occurrence of LVRR in patients undergoing this transcatheter therapy is variable.[2, 3, 18-21] For example, in the Edge-to-Edge Repair Study (EVEREST II) and the GRASP registry LV volumetric reductions at 12 months after MitraClip implantation were reported.[2, 3] However, recent studies show that not all patients undergoing TMVR achieve LVRR and a portion even develops adverse remodeling.[19, 20, 22, 23] Asch et al. recently reported that the patients included in the COAPT-trial did not show LVRR and instead increases in LV volumes were reported for the overall population[23]. However, compared to patients only receiving optimal medical treatment, the increase in LV volumes was significantly less progressive in those who underwent TMVR. Several factors may influence the occurrence of LVRR. However, knowledge of the association of preoperative LVEDD (a marker of myocardial wall stretch, and thus severity of diseased LV), with the occurrence of LVRR after TMVR are scarce. Adamo et al.[19] reported that LVEDD <75mm was associated with LVRR (defined by ≥10% reduction of LVESV) after TMVR. However, the choice of 75 mm as a cut-off was not explained. In contrast, pre- to post-operative changes of LVEDD in patients undergoing surgical mitral valve repair for secondary ischemic MR have been reported in previous studies.[4-6, 24-32] Combined ring annuloplasty and coronary revascularization have shown to induce significant LVEDD reduction in 70-80% of the patients. In the present study significant LVEDD reduction was observed in 32% of patients after TMVR. Compared to previous surgical series, this percentage is smaller and most likely can be explained by the characteristics of the patients. Patients undergoing transcatheter mitral valve repair are usually deemed non-operable, have more diseased LV and no options for additional revascularization therapy. Moreover, a relation between recurrence of MR ≥grade 2 with absence of LVRR after surgical mitral valve repair was observed in previous studies.[33, 33-37] Pre- and postoperative LV end-diastolic dimensions were larger in patients with recurrent MR, and progressive LV dilation was observed in these patients.[33-38] Consequently, cut-off values to predict LVRR or recurrent MR after surgical mitral valve repair could be identified. For example, Braun et al. assessed LVRR (defined by ≥10% reduction of LVEDD) after surgical mitral valve repair in patients with ischemic MR and previous coronary revascularization and found that LVEDD was the single best predictor for LVRR in a multivariate analyses.[4] Moreover, LVEDD <65mm had the best sensitivity and specificity of 89% (area under the curve 0.92) to predict LVRR.[4] In patients undergoing TMVR, Grayburn et al.[2] similarly showed that the absence of residual MR after TMVR was associated with LVRR. However, predictors and cut-off values to predict LVRR have yet to be identified. The present study shows that recurrence of MR grade ≥3 was less prevalent in patients with LVRR (18% vs. 29%). In addition, baseline LVEDD was associated with LVRR, which indicates this to be an important parameter at baseline. Moreover, a cut-off value similar to that proposed by Braun et al.[4] of <65mm was a strong and independent associate with LVRR.

Prognostic role of baseline parameters and LVRR

A few small sample studies have reported that the occurrence of LVRR after TMVR improved outcome, whereas the absence of LVRR was significantly associated with worse prognosis.[19-21] The present study confirmed these findings in a larger population with a long follow-up period. However, little is known of baseline characteristics associated with LVRR and outcome. The above mentioned preoperative cut-off LVEDD <65mm as an associate for LVRR in surgical mitral valve repair patients has further been identified as a strong predictor for late mortality.[6] Patients undergoing surgical mitral valve repair with a preoperative LVEDD <65mm had an 80% 5-year survival as opposed to 49% in patients with an LVEDD ≥65mm.[6] These results are important to take into account in the decision making and patient selection for surgical mitral valve repair. Patients who are deemed not suitable for surgical repair may be considered for TMVR. However, it is unknown whether certain baseline parameters, such as LVEDD <65mm, for prediction of outcome and therapy response should also be applied to patients undergoing TMVR. Recently, the COAPT-trial and MITRA-FR-trials have reported controversial results in terms of effectiveness and outcome after TMVR in addition to optimal medical treatment versus optimal medical therapy alone.[8, 39] The COAPT trial reported a significantly lower rate of hospitalizations for heart failure and all-cause mortality in the TMVR group, whereas the MITRA-FR trial showed no difference between the two groups in composite primary outcome of death or heart failure hospitalizations. Although the studies seemingly assess similar patient populations, there were important differences. Patients in the COAPT trial had less severe LV dilatation at baseline due to exclusion of patients with LVESD >70mm (101 vs. 135ml/m2). These results may suggest that the extent of LV dilatation can give an indication whether TMVR will induce LVRR and improve outcome. Also, the findings may indicate different mechanisms of secondary MR suggested by Grayburn et al.[40] The first is primarily caused by progressive LV dilatation resulting in mitral annulus dilatation with subsequent tethering of the mitral leaflets resulting in MR. These patients would benefit most from therapies targeting LV volume reduction. The second is primarily caused by dyssynchronous LV contraction (electrical or by regional wall motion abnormalities) leading to abnormal tethering of the papillary muscles and mal-coaptation. In these patients LVEDV is usually disproportionately lower than expected for the degree of MR. Therapies directly targeting the mitral valve would be most beneficial in these patients. Therefore, the degree of LV dilatation and MR severity at baseline may give an indication as to whether TMVR will induce LVRR and improve outcome or may be futile. The presents study confirms the hypothesis that the extent of LV dilatation at baseline is an important factor to take into account for patients undergoing TMVR.

Clinical implications

During the decision making prior to TMVR, it is crucial to understand which patients are most likely to achieve LVRR and who may not. The present findings show that the degree of baseline LV dilatation is an important factor most likely due to the over exhaustion of the Frank-Starling mechanism and extent of fibrosis. LVEDD may guide clinicians to first try to achieve smaller dimensions by optimising heart failure medication and/or cardiac resynchronization therapy implantation (if indicated). It may help detect patients in whom TMVR would be futile. Furthermore, recent development of several new interventional procedures may improve outcome and may be taken into account during early decision making. For example, simultaneous direct annuloplasty with for example the Cardioband may be beneficial and needs further investigation.[41, 42]

Limitations

The present study may have a selection bias since the study population was selected based on the availability of a 6-month transthoracic echocardiography, and patients who were alive within the first 6 months after implantation. Furthermore, the study sample is relatively small, leading to limited variables in the multivariate analysis, and needs to be confirmed in larger studies. In addition, the definition for LVRR is not established and varies throughout literature. We chose to use a reduction of ≥10% of the LVEDD in accordance to the study by Braun et al[4] as we aimed to assess whether the cut-off value can be validated in a group of patients who were inoperable and were treated with transcatheter mitral valve repair.

CONCLUSIONS

The capability of developing LVRR after TMVR with the MitraClip device is limited by the extent of LV dilatation prior to intervention. A baseline LVEDD <65m and development of LVRR after transcatheter mitral valve repair were associated with better event-free survival for all-cause mortality or cardiovascular hospitalization.

Reference List

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