Cardiac Remodeling Following Percutaneous Mitral Valve Repair – Initial Results Assessed by Cardiovascular Magnetic Resonance Imaging

Kardiales Remodeling nach perkutaner Mitralklappenrekonstruktion – erste Ergebnisse in der Beurteilung durch die kardiale Magnetresonanztomografie

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Key words
- heart
- Interventional procedures
- MR imaging
- artifacts
- safety
- echocardiography

Zusammenfassung


Schlussfolgerung: Die kardiale Magnetresonanztomografie erlaubt die Beurteilung kardialer Volumina bei Patienten nach MitraClip-Implanta-

Abstract

Purpose: Percutaneous mitral valve repair with the MitraClip device (Abbott Vascular, Redwood City, California, USA) is a novel therapeutic option in patients with mitral regurgitation. This study evaluated the feasibility of cardiac volume measurements by cardiovascular magnetic resonance imaging (CMR) to assess reverse myocardial remodeling in patients after MitraClip implantation.

Materials and Methods: 12 patients underwent CMR at baseline (BL) before and at 6 months follow-up (FU) after MitraClip implantation. Cine-CMR was performed in short- and long-axes for the assessment of left ventricular (LV), right ventricular (RV) and left atrial (LA) volumes.

Results: Assessment of endocardial contours was not compromised by the device-related artifact. No significant differences in observer variances were observed for LV, RV and LA volume measurements between BL and FU. LV end-diastolic (median 127 [IQR 96 – 150] vs. 112 [86 – 150] ml/m²; p = 0.03) and LV end-systolic (82 [54 – 91] vs. 69 [48 – 99] ml/m²; p = 0.03) volume indices decreased significantly from BL to FU. No significant differences were found for RV end-diastolic (94 [75 – 103] vs. 99 [77 – 123] ml/m²; p = 0.91), RV end-systolic (48 [42 – 80] vs. 51 [40 – 81] ml/m²; p = 0.48), and LA (87 [55 – 124] vs. 92 [48 – 137] ml/m²; p = 0.20) volume indices between BL and FU.

Conclusion: CMR enables the assessment of cardiac volumes in patients after MitraClip implantation. Our CMR findings indicate that percutaneous mitral valve repair results in reverse LV but not in RV or LA remodeling.

Key points:
- Volume measurements by cardiovascular magnetic resonance imaging are feasible following percutaneous mitral valve repair despite device-related artifacts.

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Severe mitral regurgitation (MR) is associated with a poor prognosis, particularly in patients with heart failure [1]. Surgical mitral valve reconstruction is the treatment of choice for symptomatic patients with severe MR [2]. The MitraClip (MC, Abbott Vascular, Redwood City, California, USA) is a novel device for percutaneous mitral valve repair that emulates the surgical edge-to-edge repair technique [3]. The device has been compared to conventional surgical approaches in selected patients suitable for surgery. First, the EVEREST I trial demonstrated feasibility, safety and efficacy with a significant reduction in MR [4]. The EVEREST II trial compared MC therapy and mitral surgery (repair or replacement) and showed superior safety and a similar clinical outcome for patients with MC therapy despite a significantly inferior reduction of MR [5]. Furthermore, echocardiography demonstrated reverse left ventricular (LV) remodeling in terms of decreased LV volumes at one-year follow-up in patients not suitable for surgery [6]. Cardiovascular magnetic resonance imaging (CMR) is currently the reference method for the assessment of cardiac volumes and function [7,8]. However, to date CMR has not been used to assess reverse remodeling after MC implantation. The MC system is CMR-capable and safe in humans up to field strengths of 3 Tesla (evaluated by Shellock R & D Services, Inc., Los Angeles, USA, http://www.mrisafety.com/) but artifacts could potentially affect delineation of endocardial contours on CMR images. Thus, this study evaluated the ability of CMR to assess reverse ventricular and atrial remodeling in patients after MC implantation.

Volumetric analysis

Endocardial and epicardial borders were manually traced on end-diastolic and end-systolic images using the semi-automatic Segment Software, version 1.8 (Medviso, Lund, Sweden) [12]. The papillary muscles were excluded from the analysis (Fig. 2). “Adequate” diagnostic image quality was defined as an image quality enabling complete delineation of ventricular and atrial endocardial boundaries. Maximum, mid-diastolic and minimum LA volumes (LAV) were calculated using the biplane area-length method [13]. All derived volumes were indexed to the patients’ body surface area using a standard formula [14], resulting in volume indices (LVEDVi, LVEF, RVEDVi, RVEF, LAVi) and stroke volume indices (LVSVi, RVSVi).

Results

A significant reduction of left ventricular volume was found in terms of beneficial, reverse left ventricular remodeling after 6-month follow-up.

No significant reduction was found in right ventricular or left atrial volumes after percutaneous mitral valve repair after 6-month follow-up.

Citation Format:

Intra- and interobserver variability

Two observers (UKR, ML) performed all CMR measurements. The first observer repeated measurements after an interval of at least one week to assess intraobserver agreement. Additional measurements were performed by a second observer to assess interobserver agreement. Both observers were blinded to the results of the first reading.

Table 1  Baseline patient characteristics.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender (67%)</td>
<td>20.3 (3 – 40)</td>
</tr>
<tr>
<td>Logistic EuroSCORE (%)</td>
<td>11.6 (0.7 – 20.7)</td>
</tr>
<tr>
<td>Hypertension (75%)</td>
<td>9 (75 %)</td>
</tr>
<tr>
<td>Hypercholesterolemia (50%)</td>
<td>6 (50 %)</td>
</tr>
<tr>
<td>Diabetes (25%)</td>
<td>4 (25 %)</td>
</tr>
<tr>
<td>Coronary artery disease (87%)</td>
<td>6 (67 %)</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease (17%)</td>
<td>2 (17 %)</td>
</tr>
<tr>
<td>Atrial fibrillation (50%)</td>
<td>6 (50 %)</td>
</tr>
<tr>
<td>Functional etiology (58%)</td>
<td>7 (58 %)</td>
</tr>
<tr>
<td>Degenerative etiology (42%)</td>
<td>5 (42 %)</td>
</tr>
</tbody>
</table>

Abbreviations: CAD = Coronary Artery Disease, EuroSCORE = European System for Cardiac Operative Risk Evaluation, STS = The Society of Thoracic Surgeons. Numbers are n (% of total number).


Statistical analysis
Statistical analysis was performed using GraphPad Prism version 5.00 for Windows (GraphPad Software, San Diego, California, USA). Normality testing was performed using the D’Agostino-Pearson omnibus method. Continuous data are presented as median and interquartile range (IQR) and were compared by Wilcoxon’s signed rank test. Categorical variables are presented as counts and percentages and were compared by McNemar’s test with the continuity correction. Bland-Altman analysis was used to assess agreement between observers. Intra- and inter-observer variances were compared between BL and FU using the F-test. Statistical significance was assumed at p < 0.05.

Results
Procedural and clinical outcomes
No severe periprocedural complications were observed. Initial device success was achieved in all patients with reduction of MR to grade 2+ in 9 patients and grade 1+ in 3 patients as assessed by echocardiography. In 10 patients 1 MC was implanted and in 2 patients 2 clips were implanted. An improvement in exertional dyspnea at 6 months by at least 1 NYHA functional class was achieved in 10 patients (83 %), and in 2 patients (17 %) no improvement in NYHA class was observed. During the follow-up period 3 patients were rehospitalized due to non-cardiac events. Detailed patient characteristics at BL and FU are presented in Table 2.

Echocardiography
Compared with baseline measurements, echocardiographic follow-up showed a non-significant reduction of LVEDVi (98 (77–135) vs. 91 (74–118) ml/m²; p = 0.5382), LVESVi (51 (33–63) vs. 48 (34–60) ml/m²; p = 1000), LVSVi (50 (47–63) vs. 41 (36–51) ml/m²; p = 0.0648) and no difference in LVEF (53 (48–57) vs. 53 (42–56) %; p = 0.6659).

CMR
CMR scanning was well tolerated by all patients at both BL and FU. There were no complications related to CMR. Echocardiography demonstrated no changes in MC device function and localization in any patient after the performance of CMR. All images were of adequate quality to enable measurement of LV, RV and LA volumes.

Intra- and interobserver variability
Intra- and interobserver biases are given in Table 3. No significant differences between BL and FU in intra- or interobserver variances were found. Intraobserver biases were small, ranging from 0.1% to 1.7% both at BL and FU. Interobserver biases were greater, varying between 0.6% and 13.7%. Variability was generally larger for LA than for ventricular measurements.

Reverse LV remodeling
Table 4 demonstrates LV variables at BL and FU by CMR. The median LVEDVi and LVESvi decreased significantly by 12% and 16%, respectively (Fig. 4). All patients showed a reduction in LVESvi and 11 of 12 (92%) patients showed a reduction in LVEDvi from BL to FU. No significant differences were found for LVSvi and LVEF.

RV and LA volumes
RV and LA volumes by CMR are shown in Table 4. No significant differences were found for RVEDvi (Fig. 5), RVSVi, RVESvi, RVEF and LA volume (Fig. 6) between BL and FU.

Discussion
To the best of our knowledge, this is the first study evaluating the use of CMR for assessing reverse remodeling in patients undergoing MC implantation. Our major findings were: First, CMR measurements of LV, RV and LA volumes are feasible in patients with implanted MC devices. Second, our CMR findings on reverse LV remodeling after MC implantation are consistent with recent data by echocardiography [5, 6]. Third, we did not observe significant changes in RV or LA volumes after MC implantation.

Intra- and interobserver variability
There is only one case report of Altijk et al. on the performance of CMR in a patient with an implanted MC device [15]. In agreement with this case report, we observed local device-related artifacts at the tips of the mitral valve leaflets in all patients. These artifacts did not affect delineation of endocardial LV or LA contours (Fig. 2, 3). However, we cannot exclude minor imprecisions at the border of the papillary muscles related to these artifacts (Fig. 2). According to guideline recommendations [11], an SSFP sequence was used for cine CMR. However, the use of Spoiled Gradient Echo (Fast Low Angle SHot = FLASH) could have resulted in a further reduction of artifact size. The variability of LV, RV and LA volumetric analyses was similar to reference values in the literature [16–19]. Regarding ventricular parameters, the highest interobserver variability was found for RVESVi, in accordance with previous reports [18–21]. This may be related to diffi-

Table 2
Changes in echocardiographic and functional variables from BL to FU.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>Follow-up</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MR severity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1+ (mild)</td>
<td>0 (0)</td>
<td>3 (25)</td>
<td>0.21</td>
</tr>
<tr>
<td>2+ (mild to moderate)</td>
<td>0 (0)</td>
<td>9 (75)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>3+ (moderate to severe)</td>
<td>8 (67)</td>
<td>0 (0)</td>
<td>0.001</td>
</tr>
<tr>
<td>4+ (severe)</td>
<td>4 (33)</td>
<td>0 (0)</td>
<td>0.09</td>
</tr>
<tr>
<td>NYHA functional class</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>0 (0)</td>
<td>1 (8)</td>
<td>1.00</td>
</tr>
<tr>
<td>II</td>
<td>1 (8)</td>
<td>9 (75)</td>
<td>0.01</td>
</tr>
<tr>
<td>III</td>
<td>11 (82)</td>
<td>2 (17)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>echocardiography parameters</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV end-diastolic volume index</td>
<td>98 (77–135)</td>
<td>91 (74–118)</td>
<td>0.54</td>
</tr>
<tr>
<td>LV end-systolic volume index</td>
<td>51 (33–63)</td>
<td>48 (34–60)</td>
<td>1.00</td>
</tr>
<tr>
<td>LV stroke volume index</td>
<td>50 (47–63)</td>
<td>41 (36–51)</td>
<td>0.06</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>53 (48–73)</td>
<td>52 (46–56)</td>
<td>0.67</td>
</tr>
</tbody>
</table>

**Abbreviations:** LV = left ventricular, LVEF = left ventricular ejection fraction, MR = mitral regurgitation, NYHA = New York Heart Association. Numbers are n (% of total column number) for categorical and median (interquartile range) for continuous data.

diastolic and end-systolic LV volumes 12 months after MC implantation. Recently, echocardiography has demonstrated a significant reduction in end-diastolic and end-systolic LV volumes after MC implantation in 2 larger cohorts of 144 and 63 patients, respectively [5, 6]. In comparison to our CMR results, echocardiography failed to demonstrate a significant reduction of LV volumes in our study population. This discrepancy can be explained by the known limitations of echocardiography as a less precise tool in LV volume analysis [23, 24]. Larger study populations are required to detect significant differences in cardiac volumes by echocardiography compared to CMR. The proof of LV remodeling after MC implantation is important in the subgroup of patients with MR and severely reduced LV function: Chronic volume overload in MR is related to remodeling of the extracardial matrix with dissolution of collagen tissue and consecutive rearrangement and slippage of myocardial fibers [25, 26]. Subsequent decomposition is characterized by progressive LV dilation, elevated diastolic LV pressure, increased systolic wall stress and reduced LV ejection fraction [27]. The poor outcome of mitral valve surgery in patients with severely reduced LV function could be potentially related to irreversible changes in the extracardial matrix as well as a result of the underlying disease such as dilative cardiomyopathy or MR itself [2]. Our CMR data on patients with a median LVEF of 35% underscore recent echocardiographic data on the potential for reverse LV remodeling after mitral valve repair in patients with MR and reduced LV function [5, 6].

### Reverse LV remodeling

The significant reduction of MR detected by echocardiography as well as of LV volumes detected by CMR underscores previous findings after percutaneous mitral valve repair. Recently, echocardiography has demonstrated a significant reduction in end-diastolic and end-systolic LV volumes 12 months after MC implantation. In comparison to our CMR results, echocardiography failed to demonstrate a significant reduction of LV volumes in our study population. This discrepancy can be explained by the known limitations of echocardiography as a less precise tool in LV volume analysis [23, 24]. Larger study populations are required to detect significant differences in cardiac volumes by echocardiography compared to CMR. The proof of LV remodeling after MC implantation is important in the subgroup of patients with MR and severely reduced LV function: Chronic volume overload in MR is related to remodeling of the extracardial matrix with dissolution of collagen tissue and consecutive rearrangement and slippage of myocardial fibers [25, 26]. Subsequent decomposition is characterized by progressive LV dilation, elevated diastolic LV pressure, increased systolic wall stress and reduced LV ejection fraction [27]. The poor outcome of mitral valve surgery in patients with severely reduced LV function could be potentially related to irreversible changes in the extracardial matrix as well as a result of the underlying disease such as dilative cardiomyopathy or MR itself [2]. Our CMR data on patients with a median LVEF of 35% underscore recent echocardiographic data on the potential for reverse LV remodeling after mitral valve repair in patients with MR and reduced LV function [5, 6].

### RV and LA remodeling

The use of CMR to assess RV and LA volumes and function following MC implantation is attractive since echocardiographic assessment of these chambers is challenging [28]. However, we did not observe significant changes in end-diastolic or end-systolic RV volumes from baseline to follow-up. This finding may be related to preserved RV function and normal RV volumes at BL in our study population. RV volumes in our study were similar to normal values from healthy subjects in the literature [16]. Thus, no further reduction in RV volumes could be expected. In contrast, one would expect reverse LA remodeling after successful reduction of MR by MC implantation. LA volume and function were recently identified as important prognostic parameters [29]. Compared to the healthy cohort of Hudsmith et al. [16], our patients had severely enlarged left atrial volumes at BL. However, we did not find a reduction in LA volume from BL to FU. This could hypothetically either be related to the 6-month follow-up interval or to possibly irreversible LA structural changes in terms of myocardial fibrosis. Several recent studies observed profound structural
changes of the LA in patients with chronic MR [30–32]. LA enlargement is accompanied by chronic inflammatory changes, cellular hypertrophy and interstitial fibrosis [33]. Thus, interstitial fibrosis in patients with chronic mitral regurgitation may result in irreversible LA dilatation. The assessment of LA fibrosis by delayed enhancement CMR could be used to evaluate this aspect and identify patients with a low likelihood of reverse LA remodeling [34]. Furthermore, 6 patients in our cohort had chronic atrial fibrillation. These patients were unlikely to experience reverse LA remodeling due to the profibrotic effect of the arrhythmia itself [35].

Limitations
This pilot study is mainly limited by its small study cohort. Of note, due to multiple testing in our small study cohort, the statistically significant results should not be interpreted as given facts and require focused testing in a larger study cohort. In addition, the observed reduction of LV volumes in our study population can be a result of regression to mean effect. Nevertheless, all patients in our study population had a reduction in LVEDVi and 92% had a reduction of LVEDVi from BL to FU. We are therefore confident that there was reverse LV remodeling in our study population in agreement with recent data of larger studies such as by Rudolph et al. [6]. An additional aspect could be the use of retrospective gating in our study population, including 50% patients with atrial fibrillation. However, image quality was sufficient in these patients, so that prospective triggering was deemed unnecessary.

Conclusion
CMR allows reproducible assessment of cardiac volumes in patients with implanted MC devices. Furthermore, CMR findings indicate that MC implantation results in reverse LV but not in RV or LA remodeling.
Clinical relevance of the study

- Volumetric analysis via CMR after percutaneous mitral valve repair is feasible despite artifacts.
- Our results of cardiac volumetric analysis indicate that after a period of 6 months percutaneous mitral valve repair results in significant reduction of left ventricular volumes in terms of favorable reverse remodeling but not in significant changes of right ventricular or left ventricular volumes.

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