MRI to Evaluate Left Atrial and Ventricular Reverse Remodeling After Restrictive Mitral Annuloplasty in Dilated Cardiomyopathy

Jos J.M. Westenberg, PhD; Rob J. van der Geest, MSc; Hildo J. Lamb, MD, PhD; Michel I.M. Versteegh, MD; Jerry Braun, MD; Joost Doornbos, PhD; Albert de Roos, MD, PhD; Ernst E. van der Wall, MD, PhD; Robert A.E. Dion, MD, PhD; Johan H.C. Reiber, PhD; Jeroen J. Bax MD, PhD

Background—Data on reverse remodeling of the left atrium (LA) and left ventricle (LV) after restrictive annuloplasty in patients with dilated cardiomyopathy are scarce, and follow-up studies are performed with echocardiography.

Methods and Results—Twenty patients with dilated cardiomyopathy and severe mitral regurgitation selected for restrictive mitral annuloplasty underwent serial MRI studies (within 1 week before surgery, and 2 months \([n = 18]\) and 1 year \([n = 13]\) after surgery). Early mortality was 10%; all patients were free from endocarditis and thromboembolism. New York Heart Association class improved from 3.2±0.4 to 1.2±0.9. Only 1 patient developed recurrent severe mitral regurgitation during follow-up and it was re-repaired. LA end-systolic volumes decreased significantly over time (from 165±48 mL to 109±23 mL to 111±28 mL; \(P<0.01\)), as did LA end-diastolic volumes (from 92±32 mL to 71±22 mL to 75±17 mL; \(P=0.01\)). LV end-diastolic volumes decreased significantly (from 244±56 mL to 184±54 mL to 195±67 mL; \(P<0.01\)), whereas end-systolic volumes did not change significantly. LV ejection fraction increased significantly (from 35±8% to 46±13% to 46±15%; \(P<0.01\)) and LV mass decreased significantly (from 150±43 grams to 132±39 grams to 136±33 grams; \(P=0.02\)).

Conclusion—Restrictive annuloplasty in patients with dilated cardiomyopathy yielded excellent clinical results associated with significant LA and LV reverse remodeling over time as demonstrated by MRI. (Circulation. 2005;112[suppl I]:I-437–I-442.)

Key Words: remodeling ■ mitral valve ■ magnetic resonance imaging ■ regurgitation ■ cardiac volume

Mitral regurgitation is a significant complication of dilated cardiomyopathy and is considered to be secondary to annular dilatation and altered geometry of the left ventricle (LV).1,2 Regurgitation results in volume overload of the left atrium (LA) during systole, followed by LA and LV dilatation (remodeling) with further progressive mitral regurgitation.2,3 This condition is associated with high morbidity and mortality when treated conservatively.4,5 Heart transplantation is the preferred treatment for patients with end-stage cardiomyopathy, but the number of donor hearts is limited. In these patients, surgical mitral valve repair may be preferred, although associated with an increased (peri-)operative morbidity and mortality.

Currently, follow-up data of LA and LV reverse remodeling after surgical correction of mitral regurgitation in patients with heart failure caused by dilated cardiomyopathy are scarce. Bolling et al6 have reported on short-term and mid-term survival and LV reverse remodeling after restrictive mitral annuloplasty, without information on LA reverse remodeling. Besides the limited information on LA and LV reverse remodeling, the follow-up studies are performed by echocardiography, which is not optimal for precise assessment of LA and LV volumes. MRI is yet another noninvasive imaging technique and is currently considered the gold standard for assessment of LV function and volumes.7 Advantages of MRI over echocardiography are the superior image quality and quantification possibilities with high reproducibility, implying smaller sample sizes will be sufficient to prove statistical significance.8 Rajappan et al9 suggested that MRI is ideal for accurate and reproducible serial assessment of LV remodeling in patients with heart failure.

In the present study, serial MRI studies are performed to optimally and quantitatively assess the effects of mitral valve repair on both LA and LV reverse remodeling in dilated
We have evaluated 20 patients with dilated cardiomyopathy and severe mitral regurgitation who underwent restrictive annuloplasty. Serial MRI studies were performed: a baseline study 1 week before surgery, and 2 follow-up studies at 2 months and 1 year after surgery.

Materials and Methods

Patients and Study Protocol

The study population consisted of 20 consecutive patients (14 male, 6 female, mean age 52 ± 13 years) scheduled for mitral valve repair; all had dilated nonischemic cardiomyopathy (coronary artery disease excluded on coronary angiography) and severe (grade 3 to 4+) mitral regurgitation on echocardiography. Patients with coronary artery disease, primary organic mitral valve disease, prosthetic valves, pacemakers/defibrillators, intracranial clips, and (supra-)aortic lesions were excluded.

All patients presented with heart failure (16 [80%] in New York Heart Association [NYHA] class III and 4 [20%] in class IV). The baseline characteristics are summarized in Table 1.

Mitral Valve Surgery

The procedure was performed on normothermic cardiopulmonary bypass with intermittent antegrade warm blood cardioplegia through median sternotomy and a transthoracic approach. All patients underwent a stringent restrictive annuloplasty (downsizing the annulus by 2 sizes) with the implantation of an undersized semi-rigid ring (Carpentier-Edwards Physiopoint; Edwards Lifesciences, Irvine, Calif).

Echocardiography

Thoracic (TTE) and transesophageal echocardiography (TEE) were performed within 1 week before surgery. TEE was performed without general anesthesia to avoid underestimation of severity of regurgitation. For the TTE, patients were imaged in the left lateral decubitus position using a commercially available system (Vingmed Vivid Seven; General Electric-Vingmed, Milwaukee, Wisc). Images were obtained using a 3.5-MHz transducer at a depth of 16 cm in the parastral and apical views (standard long-axis, 2-chamber, and 4-chamber images). The severity of mitral regurgitation was graded semi-quantitatively from color-flow Doppler in the conventional parasternal long-axis and apical 4-chamber images, and characterized as follows: mild, 1+ (ratio jet area/LA area <10%); moderate, 2+ (jet area/LA area 10% to 20%); moderately severe, 3+ (jet area/LA area 20% to 45%); and severe, 4+ (jet area/LA area >45%). All patients had 3 to 4+ mitral regurgitation (central jet) secondary to LV and annular dilatation and systolic restrictive motion of mitral leaflets (Carpentier type IIIb). Immediately after the TTE, a TEE was performed to assess residual regurgitation, transmitial diastolic gradient (determined from continuous-wave Doppler), mitral valve area (by direct planimetry), and length of coaptation of the mitral valve leaflets. TEE was repeated at 1-year follow-up, and similar parameters were assessed.

MRI

To assess LA/LV volumes and LV ejection fraction (EF), serial MRI studies (1 week before surgery, 2 months and 1 year after surgery) were performed with a 1.5-T MRI scanner (ACS-NT15 Gyroscan with the Powertrack 6000 gradient system; Philips Medical Systems, Best, the Netherlands) using the body coil for transmission and a 5-element phased-array synergy cardiac coil placed on the chest for signal reception. Standard 2-chamber and 4-chamber long-axis series and a complete set of short-axis cine acquisitions were performed (conform standard cardiac MR protocols using balanced FFE) with the patient performing a breath-hold in end expiration. Imaging parameters of the 2-chamber and 4-chamber long-axis series as well as for the short-axis series: TE/TR = 1.52/3.0, flip angle = 50°, field of view = 350 mm, scan matrix = 192 × 192, slice thickness = 8 mm, and gated cardiac triggering with retrospective reconstruction of 30 phases. For the short-axis series, 10 to 12 parallel oriented slices were acquired with a 2-mm slice gap, one slice for each breath-hold. End-diastolic volume (EDV) and end-systolic volume ( ESV) were obtained both for the LV (from short-axis MRI) and the LA (from measuring biplane area length in orthogonal long-axis 2-chamber and 4-chamber views) by manual segmentation performed by one observer. Image analysis was performed blinded with respect to the pre-surgery data. Significant reverse remodeling was defined as a reduction in volumes ≥15%.

LV measurements (EDV, ESV, LVEF, LV mass) from short-axis are reported to be reproducible. The reproducibility of LA volume measurements with biplane area-length in long-axis MR images was studied by Sievers et al. Intra- and inter-observer variations of our image analysis were determined by repeated analysis by one observer (blinded to the first analysis with an interval >1 month) and additional image analysis of a second observer (blinded to the results from the first observer).

Aortic flow measurements were obtained from velocity-encoded MRI to determine the true stroke volume (SV). To correct for the effect of mitral regurgitation on LVEF, the LVEF was derived by calculating the ratio SV/EDV. MRI Mass and Flow software (Medis, Leiden, the Netherlands) were used for image analysis. An increase in LVEF ≥5% and a decrease in LV mass ≥10 grams were considered significant.

Statistical Analysis

Continuous data were expressed as mean ± SD and compared using the Student t test for paired data. P < 0.05 was considered significant. Intra- and inter-observer variation was studied by calculating the coefficient of variation (defined as the standard deviation of the differences between the two series of measurement divided by the mean of both measurements) with confidence interval.

Results

Surgical and Clinical Results

One patient died during surgery and one patient died within 2 months after surgery because of refractory heart failure. No follow-up data of these 2 patients were acquired and they were excluded from the MRI analysis. The remaining 18 patients experienced no complications during surgery. Mean cardiopulmonary bypass time was 141 ± 26 minutes and mean ischemic time was 96 ± 27 minutes. The mean annuloplasty ring size was 28 ± 2 mm (range, 24 to 30 mm). None of the patients underwent concomitant tricuspid annuloplasty. TEE immediately after surgery demonstrated minimal regurgitation (grade ≤1+) in 2 patients, whereas the remaining 18 patients had no residual regurgitation. On average, the patients had grade 0.1 ± 0.3 mitral regurgitation. The mean length of coaptation was 0.8 ± 0.4 cm (range 0.6 to 1.0 cm). The mean transmitial diastolic gradient was 2.7 ± 0.6 mm Hg (range, 1.2 to 3.8 mm Hg). Systolic anterior movement of the

---

**TABLE 1. Patient Characteristics (n=20)**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>52±13</td>
</tr>
<tr>
<td>Gender, M/F</td>
<td>14/6</td>
</tr>
<tr>
<td>NYHA Class</td>
<td>3.2±0.4</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>35±8</td>
</tr>
<tr>
<td>Grade mitral regurgitation</td>
<td>3.4±0.5</td>
</tr>
<tr>
<td>Coaptation, cm</td>
<td>0.3±0.2</td>
</tr>
</tbody>
</table>

LVEF indicates left ventricular ejection fraction; NYHA, New York Heart Association.
One-year survival was 90%. None of the surviving patients experienced endocarditis or thromboembolic events. One patient over time had a grade 3+ mitral regurgitation and benefited from a repeat repair. At 1-year follow-up mitral regurgitation was grade 0.4/H11006 versus immediately after surgery). NYHA class had improved to 1.2/H11006 versus immediately after surgery). The mean transmitral diastolic gradient was 2.8/H11006 mm Hg (range, 1.5 to 3.8 mm Hg, NS versus immediately after surgery). The mitral valve area was 2.9/H11006 cm² (range, 2.2 to 3.8 cm², nonsignificant [NS] versus immediately after surgery). NYHA class had improved to 1.2/H11006 versus 0.9 with all patients in class I or II, except for the patient who had grade 3+ mitral regurgitation, who was in NYHA class III before the re-repair.

LA and LV Volumes: Assessment by MRI

In Figure 1, a patient example illustrating the LA and LV reverse remodeling assessed by MRI is shown. All surviving patients were included in the 2-month follow-up and 13 patients were included in the 1-year follow-up. All MRI results are summarized in Table 2. LAEDV decreased significantly from 92±32 mL to 71±22 mL (P<0.01) and remaining on 111±28 mL (P=0.81). On a patient basis, significant LA reverse remodeling (predefined by a reduction ≥15% in volume) for ESV occurred in 78% of the patients, with 72% showing early reverse remodeling and 6% showing late reverse remodeling; the individual data are presented in Figure 2 (right panel).

LVEDV decreased significantly from 244±56 mL to 184±54 mL (P<0.01) and increased insignificantly to 195±67 mL (P=0.58). Significant reverse remodeling of EDV occurred in the majority of patients (67%) at early follow-up, whereas 11% exhibited reverse remodeling only at late follow-up. The individual data are shown in Figure 3 (left panel). In the entire group, LVESV did not change significantly at early or late follow-up (94±39 mL versus 88±55 mL [P=0.50] versus 96±72 mL [P=0.28]), but on a patient basis, 50% showed significant reverse remodeling of ESV at early (44%) or late (6%) follow-up. The individual results are shown in Figure 3 (right panel).

Table 2. MRI Results Before Surgery and at 2-Month and 1-Year Follow-up

<table>
<thead>
<tr>
<th></th>
<th>Before Surgery</th>
<th>P</th>
<th>2-Month Follow-up</th>
<th>P</th>
<th>1-Year Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAESV, mL</td>
<td>165±48</td>
<td>&lt;0.01</td>
<td>109±23</td>
<td>0.81</td>
<td>111±28</td>
</tr>
<tr>
<td>LAEDV, mL</td>
<td>92±32</td>
<td>0.01</td>
<td>71±22</td>
<td>0.46</td>
<td>75±17</td>
</tr>
<tr>
<td>LVEDV, mL</td>
<td>94±39</td>
<td>0.50</td>
<td>88±55</td>
<td>0.28</td>
<td>96±70</td>
</tr>
<tr>
<td>LVESV, mL</td>
<td>244±56</td>
<td>&lt;0.01</td>
<td>184±54</td>
<td>0.58</td>
<td>195±67</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>35±8</td>
<td>&lt;0.01</td>
<td>46±13</td>
<td>0.26</td>
<td>46±15</td>
</tr>
<tr>
<td>LV mass, grams</td>
<td>150±43</td>
<td>0.02</td>
<td>132±39</td>
<td>0.15</td>
<td>136±33</td>
</tr>
</tbody>
</table>

EDV indicates end-diastolic volume; EF, ejection fraction; ESV, end-systolic volume; LA, left atrium; LV, left ventricle.
Overall, 78% of the patients showed early or late LA reverse remodeling as well as 78% of the patients showed early or late LV reverse remodeling. Only one patient (6%) did not show any (early or late) reverse remodeling.

LVEF increased significantly over time: from 35 ± 8% at baseline to 46 ± 13% (P < 0.01) at early follow-up and remained on 46 ± 15% at late follow-up (P = 0.26). Of note, 72% of patients showed a significant increase in LVEF (predefined as an increase in LVEF ≥ 5%) at early follow-up, whereas 6% only showed an increase at late follow-up; individual results are shown in Figure 4 (left panel). One patient showed recurrent mitral regurgitation and was in NYHA class III at late follow-up; this patient showed a decrease in LVEF from 12% at baseline to 7% at 1-year follow-up.

LV mass showed a statistically early significant decrease (predefined by a reduction ≥ 10 grams): from 150 ± 43 g to 132 ± 39 grams (P = 0.02) and remaining on 136 ± 33 grams (P = 0.15). In addition, 67% of the patients showed a significant decrease in LV mass at early follow-up, whereas 6% showed a significant decrease at late follow-up; individual data are presented in Figure 4 (right panel).

Intra- and inter-observer variations of LAEDV and LAESV measurements were determined by repeated analysis by the same observer and one additional observer. The results are presented in Table 3. The coefficient of variation (defined as the standard deviation of the differences between the 2 series of measurements divided by the mean of both measurements) never exceeded 5% for both intra- as well as inter-observer variation.

Discussion

In patients with severe mitral regurgitation, conservative management is associated with poor prognosis. One-year survival of 30% to 40% is reported for patients with dilated cardiomyopathy with severe mitral regurgitation. However, surgical intervention is associated with an increased (peri-) operative morbidity and mortality. Bolling et al6 have demonstrated the feasibility of mitral valve repair by downsizing the annulus using a flexible ring. Their results showed a 75% 1-year survival for patients undergoing restrictive valve repair. Gummert et al reported a 1-year survival of 86% (80% of the patients had nonischemic dilated cardiomyopathy). Szalay et al17 reported an early mortality of 6.6% with an 85% survival at 2 years, although most of the patients had ischemic cardiomyopathy and only 30% had nonischemic dilated cardiomyopathy. The results of the current study (for nonischemic dilated cardiomyopathy only), with 10% early mortality without late cardiac deaths, are in line with the previous studies. At 1-year follow-up, all patients in the current study had improved significantly in symptoms, with only one patient in NYHA class III who had severe recurrent mitral regurgitation. Our results are in agreement with the previous studies.6,16,17 Szalay et al17 reported an improvement in NYHA class from 3.3 ± 0.1 at baseline to 1.8 ± 0.2 at 2-year follow-up.

In the present study, surgical repair with restrictive annuloplasty was successful in 17 of 20 patients (85%) without recurrence of significant mitral regurgitation at late follow-up, with restoration of leaflet coaptation without introducing mitral valve stenosis. Similar results were obtained in previous studies.6,16,17 Bolling et al8 reported mild regurgitation for 19% of patients 1 week after surgery and no regurgitation for 81% of the patients. Similarly, Szalay et al17 reported recurrent mitral regurgitation in 3.3% of the patients, with a mean mitral regurgitation grade 0.6 at 1-year follow-up.

Besides the improvement in clinical status, previous studies demonstrated LV reverse remodeling and improvement in LVEF after mitral valve repair. Bolling et al2 hypothesized that stabilization of the mitral annulus and unloading of the
LV may be responsible for the improvement in LVEF and the reverse remodeling. These issues are clinically relevant, because a reduction of LV dimensions and an increase in LVEF are associated with a favorable prognosis.\textsuperscript{18,19} In the current study, LVEF increased significantly from 35\%\textpm{}8\% at baseline to 46\%\textpm{}15\% at 1-year follow-up. Similarly, Bolling et al\textsuperscript{6} showed an increase in LVEF from 18\%\textpm{}5\% to 24\%\textpm{}10\%, and Gummert et al\textsuperscript{16} showed an improvement of 25\%\textpm{}11\% to 34\%\textpm{}15\% at 2-year follow-up. In addition, reverse remodeling was observed in the current study. The mean LVEDV decreased significantly over time, although LVESV did not exhibit a decrease in the entire study population. Still, on a patient basis, 50\% of patients showed significant reduction in LVESV over time. The previous studies\textsuperscript{16,17,19} did not assess LV volumes but demonstrated a significant decrease in LV dimensions. Of note, in the present study, LV reverse remodeling was observed at early follow-up in the majority of the patients, but a substantial percentage of patients showed reverse remodeling only at late follow-up. These findings indicate that the process of reverse remodeling may need substantial time in some patients.

LV dimensions and LVEF have prognostic value,\textsuperscript{18,19} but also LA dimensions are important prognostic parameters.\textsuperscript{20,21} In the present study, both LAEDV and LAESV showed a significant decrease over time and occurred in most (78\%) of the patients. To the best of our knowledge, no previous studies have reported on LA reverse remodeling after mitral valve repair.

All previous studies were performed with echocardiography, which is limited by substantial intra- and inter-observer variations and geometric assumptions needed for quantification. In the present study, MRI was used to assess LA and LV volumes. LV volume measurement with MRI is reported to be accurate and reproducible.\textsuperscript{13} LA volume measurements with biplane area-length in long-axis MR images provide reproducible results in clinical practice.\textsuperscript{14} The intra- and inter-observer variations for the data analysis of the current study are very low (ie, not exceeding 5\% in volume measurements). The criterion used for reverse remodeling definition (ie, volume increase $\geq$15\%) amply exceeds the observer variations.

MRI has a superior image quality as compared with echocardiography and is not hampered by technical limitations such as suboptimal acoustic windows. MRI has the advantage of acquiring every arbitrary double-obliquely–oriented imaging plane 3-dimensionally. MRI is currently considered the gold standard for assessment of LA and LV volumes, and its noninvasive character and high reproducibility make this technique ideal for follow-up studies after therapy.\textsuperscript{22} Moreover, the high reproducibility allows for smaller study sample sizes to prove statistical significance. For example, to demonstrate a 10-mL difference in EDV and ESV with $P<0.05$ and a power of 90\%, only 12 and 10 patients, respectively, are sufficient to include in an MRI study. With echocardiography, 121 and 53 patients, respectively, would be required to prove significant differences.\textsuperscript{8} In the current study, significant LA and LV reverse remodeling was statistically significantly proven already with only 18 patients and 13 patients included in the 2-month and 1-year follow-up, respectively.

Limitations

Some patients cannot undergo MRI; claustrophobia is occasionally a problem, and absolute contraindications include pacemakers, defibrillators, and cerebral clips. Scanning patients with sternal wires and an implanted restrictive mitral annulus ring is safe and the associated signal loss from the paramagnetic material does not hamper image analysis. In the current study, only patients with nonischemic cardiomyopathy were included; additional studies in patients with ischemic cardiomyopathy are needed.

Conclusions

MRI showed significant LA and LV reverse remodeling in patients with nonischemic dilated cardiomyopathy and severe

\begin{table}
\centering
\caption{Intra- and Inter-observer Variation Study of ED and ES Volume Measurements of Left Atrium With Biplane Area Length}
\begin{tabular}{lcccc}
\hline
 & EDV & ESV & EDV & ESV \\
 & Intra-observer & Intra-observer & Inter-observer & Inter-observer \\
\hline
Coefficient of variation & 4\% & 5\% & 5\% & 5\% \\
Confidence interval & $-8$ mL--12 mL & $-18$ mL--24 mL & $-6$ mL--14 mL & $-12$ mL--25 mL \\
P value & 0.76 & 0.35 & 0.06 & 0.14 \\
\hline
\end{tabular}
\end{table}
mitral regurgitation who underwent restrictive mitral annuloplasty. In particular, 78% of patients showed reverse remodeling of the LA and LV. Moreover, LVEF improved significantly in 78% of the patients with a reduction in LV mass in 72%.

Acknowledgments

Financial support by the Netherlands Heart Foundation, grant 99.099, is gratefully acknowledged.

References

MRI to Evaluate Left Atrial and Ventricular Reverse Remodeling After Restrictive Mitral Annuloplasty in Dilated Cardiomyopathy
Jos J.M. Westenberg, Rob J. van der Geest, Hildo J. Lamb, Michel I.M. Versteegh, Jerry Braun, Joost Doornbos, Albert de Roos, Ernst E. van der Wall, Robert A.E. Dion, Johan H.C. Reiber and Jeroen J. Bax

_Circulation_. 2005;112:I-437-I-442
doi: 10.1161/CIRCULATIONAHA.104.525659

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2005 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/112/9_suppl/I-437

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org/subscriptions/