Changes in Mitral Annular Geometry and Dynamics With β-Blockade in Patients With Degenerative Mitral Valve Disease

Daniel B. Ennis, PhD; Gabriel R. Rudd-Barnard, MS; Bo Li, PhD; Carissa G. Fonseca, PhD; Alistair A. Young, PhD; Brett R. Cowan, MBChB; Ralph A.H. Stewart, MD

Background—Remodeling of the mitral annulus contributes to progression of mitral regurgitation (MR). In patients with moderate-to-severe MR, short-term treatment with β-blockers has been shown to increase left ventricular (LV) end-diastolic and end-systolic volume, and this could deleteriously increase mitral valve annular dimensions. The objective of this study was to quantify the effects of a short duration of β-blocker treatment on mitral annular dimensions and dynamics in patients with MR due to primary degenerative valve disease.

Methods and Results—Twenty-five patients with moderate-to-severe degenerative MR and normal LV systolic function were studied in a double-blind crossover experiment using a β1-selective adrenergic blocker and placebo administered for 14±3 days. Cardiac MRI images were acquired after each treatment period to quantify mitral annular dimensions. At end diastole, there was no change in annular area (1659±331 versus 1632±299 mm²; P<0.19), annular perimeter (154.3±16.4 versus 152±13.9 mm; P<0.13), septal-lateral (SL) dimension (38.0±5 versus 39.0±4.5 mm; P<0.15), or annular height (9.8±3.8 versus 9.5±2.5 mm; P<0.53). β-blockade resulted in significant end-diastole decreases in commissure-commissure dimension (48.9±4.6 versus 47.2±4.0 mm; P<0.01) and eccentricity (1.3±0.2 versus 1.2±0.1; P<0.01). At end systole (ES), β-blockade conferred a small, but significant decrease in annular perimeter (161.0±19.3 versus 156.8±16.9 mm; P<0.04) and eccentricity (1.2±0.1 versus 1.1±0.1; P<0.02), and the SL dimension significantly increased (41.5±5.7 versus 43.0±5.3 mm; P<0.03). Commissure-commissure dimension, annular area, and annular height at ES were not significantly different.

Conclusions—Despite significant increases in LV end-diastolic and end-systolic volume, short-term β-blocker treatment of patients with moderate-to-severe MR reduced or preserved all mitral annular dimensions except SL at ES. (Circ Cardiovasc Imaging. 2010;3:687-693.)

Key Words: mitral valve ▪ regurgitation ▪ beta blockers adrenergic

Primary mitral regurgitation (MR), which usually is caused by myxomatous degeneration of the mitral valve (MV) leaflets, leads to a progressive increase in left ventricular (LV) volume. Eventually, this may result in LV dysfunction and heart failure. Current guidelines recommend MV repair or replacement in patients with chronic severe MR who have symptoms or evidence of LV dysfunction. Surgery also may be considered in asymptomatic patients with normal LV function who have a repairable valve because of a high risk of disease progression and adverse outcomes. However, many asymptomatic patients with moderate-to-severe MR are not referred for early surgery, and in these patients, a medical treatment that reduces the risk of disease progression would be beneficial. The clinical management of patients with chronic primary MR, however, remains contentious.

In a retrospective observational study by Varadarajan et al of 895 patients with severe ischemic or nonischemic MV regurgitation and a normal LV ejection fraction, mortality was lower for patients treated with a β-blocker. This benefit might be related to a favorable effect of the β-blocker on LV function, as observed in patients with heart failure. Alternatively, β-blockers could influence the progression of MR. MV annular dilation is one cause of the progression of MR severity. In patients with nonischemic dilated cardiomyopathy, mild-to-moderate heart failure and severe MR surgical ring annuloplasty results in reverse LV remodeling. No similar data are currently available in patients with primary MR. In patients with heart failure, β-blockers reduce the

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severity of MR, probably by a favorable effect on LV remodeling. In a previous report, we described the effects of short-term treatment with a β-blocker in patients with moderate-to-severe MR and normal LV function. In that study, β-blockers reduced LV work and mitral regurgitant volume per minute, but mitral regurgitant volume per beat did not change. β-blockers, however, also increased LV end-diastolic volume (EDV) and end-systolic (ESV), which because of annular-ventricular continuity could have an adverse effect on mitral annular dimensions. The impact of β-blockers on MV annular dimensions and dynamics in patients with degenerative MV disease and chronic MR. We hypothesized that in patients with MR, acute treatment with β-blockers will decrease annular dimensions despite an increase in LVEDV and LVESV.

Methods

Patient Population

Patients were recruited if they had moderate-to-severe MR without New York Heart Association class III or IV symptoms for heart failure. MR in all patients was caused by primary degenerative disease. Two subjects had anterior leaflet, 14 posterior leaflet, and 9 bileaflet prolapse. Eleven subjects had a flail or partial flail mitral leaflet. All patients had normal LV function defined as an ejection fraction >55% as determined by a 2D echocardiography screening examination. MR grade was characterized by either vena contracta width >3 mm, regurgitant volume >30 mL/beat, or an effective regurgitant orifice area >0.2 cm² on Doppler echocardiography. Exclusion criteria were previous myocardial infarction, renal or respiratory disease, any other valvular disease, or contraindication to inhibiting medication. All patients were in normal sinus rhythm. The majority (n = 21) were men. The average body mass index was 25.8 ± 3.8 kg/m². Twelve (48%) subjects had a history of hypertension, and 11 (44%) were on angiotensin-converting enzyme-inhibiting medication. All patients were in normal sinus rhythm. The majority (n = 18) of patients were asymptomatic, but 7 had New York Heart Association class IIa symptoms.

Study Design

Enrolled patients were studied in a double-blind crossover experiment using the β1-adrenergic receptor blocker metoprolol on MV annular dimensions and dynamics in patients with degenerative MV disease and chronic MR. We hypothesized that in patients with MR, acute treatment with β-blockers will decrease annular dimensions despite an increase in LVEDV and LVESV.

Data Analysis

End-diastolic (ED) and end-systolic (ES) cardiac phases were identified as coincident with MV closure (ED) and aortic valve closure (ES) from the long-axis images. Two MV annular points where the valve leaflet attaches to the wall were identified in each long-axis view at ED, and custom nonrigid registration software automatically tracked the remaining points through all phases of the cardiac cycle (Figure 1). Image features were tracked automatically throughout the cardiac cycle by finding the optimal nonlinear warp between successive frames on the basis of a pixel sum-of-squared-differences metric. This software has been validated for tracking epicardial and endocardial LV contours for the assessment of LV wall mass and volumes.

Validation of the custom nonrigid registration software for tracking mitral annular points was performed for the first time as part of this study. Bland-Altman analysis was used to assess the quality of the automatic tracking of MV points. An expert observer (D.B.E.) identified 2 mitral annular points in both the ED and the ES images in each of the 6 long-axis views, and custom software recorded the 2D image pixel coordinates. The ED points were used as an input to the automatic tracking software, which returned an estimate of the annular points at ES (ES-EST). Similarly, the hand-picked ES points were used as inputs to the automatic tracking software to estimate the position of the annular points at ED (ED-EST). The 3D scanner coordinates of each point were projected onto a local radial and longitudinal coordinate system. The longitudinal direction was defined as a unit vector pointing along an axis from the LV apex to the centroid of the MV. The radial direction was defined as a unit vector pointing from each annular point along a direction orthogonal to the longitudinal direction. The difference (ED-ED-EST and ES-ES-EST) and the average (mean of ED and ED-EST and the mean of ES and ES-EST) of the recorded radial and longitudinal coordinate results obtained by the expert and the automatic tracking software were used to construct a Bland-Altman figure to calculate the bias and the limits of agreement (95% CIs).

Each of the 12 identified points on the MV annulus at ED and ES were converted from image coordinates to scanner coordinates in order to create a 3D model of the annulus at each cardiac phase. The model was created independently for each cardiac phase using a cubic interpolating (nonsmoothing) spline that incorporated each of the 12 annular points. Annular perimeter was measured by summing the distance between densely spaced points along the spline. Annular area was calculated by summing the area of small triangles that adjacent points along the annular spline made with the centroid of the annulus.

Figure 2 shows an example model of the mitral annulus with labeled anatomic points. The most superior point nearest the aorto-mitral juncture was identified as the saddlehorn (SH). A short-axis image at the level of the MV plane was used to identify mitral annular points nearest the anterior (ACOM) and posterior (PCOM) MV commissures. The commissure-mississure (CC) axis was defined as a line from the ACOM to the PCOM. The point on the annulus opposite the SH point along a line perpendicular to the CC axis was defined as the cantile (CA). The septal-lateral (SL) and CC dimensions were measured as the Euclidean distance from SH to CA and PCOM to ACOM, respectively. Mitral annular eccentricity was calculated as the ratio of CC to SL (Figure 3).
To estimate the mitral annular height, a plane was fitted using linear least-squares regression to the 12 markers at each cardiac phase. The mitral annular height was defined as the sum of the perpendicular distance from the SH (most superior point) to the fit-plane plus the perpendicular distance from the most inferior marker to the fit-plane (Figure 3).

To compare β-blocker-induced changes in mitral annular dimensions (SL and CC) to the corresponding changes in LV dimensions, the LV diameter along the SL and CC axes was extracted at ED and ES at a level one third below the base of the heart. Correlation coefficients at ED and ES were calculated between annular and ventricular SL and CC changes (BB-PL). The correlation coefficient between each mitral annular geometric measure and mitral regurgitant volume per minute was also calculated. Lastly, the correlation between the change in regurgitant volume per minute (PL-BB) and PL mitral regurgitant volume per minute was calculated.

The dynamic data for each measured parameter was temporally resampled with interpolating splines during the diastolic and systolic intervals to facilitate comparison of events among patients despite a range of patient heart rates. The data for each subject and each measure between aortic valve closure (beginning of diastole) and MV closure (ED) were resampled to the first one third of the cardiac cycle, and data between MV closure (beginning of systole) and aortic valve closure (ES) were resampled to the remaining two thirds of the cardiac cycle.

Statistical results for each of the measured variables and the within-subject differences are reported as mean±SD. Two-tailed paired t tests were used to identify the statistical differences in annular dimensions and dynamics between the PL and BB treatment groups. P<0.05 was considered statistically significant. Intra- and interobserver coefficients of variation (SD of the differences divided by the mean of the measures) were calculated for each parameter.

**Results**

**Image Quality and Point Tracking**

Figure 1 provides examples of the images acquired and analyzed for the study. All 50 examinations resulted in high-quality images that were acceptable for automatic quantitative image processing and clinical evaluation. Figure 1 also demonstrates the quality and accuracy of the automatic feature tracking software, wherein expertly selected points at...
Effects of β-Blocker Treatment on LV Function

As previously reported,6 2 weeks of β-blocker treatment resulted in significant chronotropic and inotropic effects; heart rate was decreased (65 ± 10 versus 55 ± 7 beats/min; P < 0.0001), and systolic blood pressure was decreased (138 ± 18 versus 123 ± 14 mm Hg; P < 0.0001). Furthermore, administration of β-blockers resulted in significant increases in LVESV (81 ± 21 versus 85 ± 21 mL; P < 0.01) and LVEDV (229 ± 50 versus 235 ± 48 mL; P < 0.003) and a significant increase in forward stroke volume (89 ± 21 versus 94 ± 20 mL; P < 0.03). LV ejection fraction and regurgitant volume did not change significantly.

Table. MV Annular Dimensions

<table>
<thead>
<tr>
<th>Dimension</th>
<th>PL</th>
<th>BB</th>
<th>Δ</th>
<th>P</th>
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<tr>
<td>ED</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SL, mm</td>
<td>38.0±5.0</td>
<td>39.0±4.5</td>
<td>1.0±3.2</td>
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<td>CC, mm</td>
<td>48.9±4.6</td>
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<td>Perimeter, mm</td>
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<td>152.0±13.9</td>
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<td>0.13</td>
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<td>Area, cm</td>
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<td>Height, mm</td>
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<td>9.5±2.5</td>
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<td>0.53</td>
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<td>Eccentricity</td>
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<td>1.2±0.1</td>
<td>0.1±0.1</td>
<td>0.01*</td>
</tr>
<tr>
<td>ES</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SL, mm</td>
<td>41.5±5.7</td>
<td>43.0±5.3</td>
<td>1.5±3.1</td>
<td>0.03*</td>
</tr>
<tr>
<td>CC, mm</td>
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<td>45.9±5.2</td>
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<td>Perimeter, mm</td>
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<td>Area, cm</td>
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<td>Height, mm</td>
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<td>0.33</td>
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<td>−0.1±0.2</td>
<td>0.02*</td>
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</table>

Data are presented as mean ± SD for each measure, and the within-subject differences (Δ) are shown. *P < 0.05.

Effects of β-Blocker Treatment on Annular Dimensions

Mitral annular dimensions at ED and ES are reported in the Table. At ED, annular area (16.6±3.3 versus 16.3±3.0 mm²; P < 0.019), annular perimeter (154.3±16.4 versus 152±13.9 mm; P < 0.13), SL (38.0±5.5 mm versus 39.0±4.5 mm; P < 0.15), and annular height (9.8±3.8 versus 9.5±2.5 mm; P < 0.53) did not increase after 2-week administration of β-blockers. β-blocker administration did result in significant ED decreases in CC (48.9±4.6 versus 47.2±4.0 mm; P < 0.01) and eccentricity (1.3±0.2 versus 1.2±0.1; P < 0.01).

At ES, β-blockade conferred a significant decrease relative to PL in annular perimeter (161.0±19.3 versus 156.8±16.9 mm; P < 0.04) and eccentricity (1.2±0.1 versus 1.1±0.1; P < 0.02). The SL dimension significantly increased in BB at ES (41.5±5.7 versus 43.0±5.3 mm; P < 0.03). CC (47.5±4.8 versus 45.9±5.2 mm; P < 0.08), annular area (18.1±3.7 versus 17.5±3.7 mm²; P < 0.06), and annular height (11.5±4.5 versus 10.9±3.0 mm; P < 0.33) also decreased at ES, but none were statistically significant.

The correlation coefficient between the change in mitral annular SL and LV SL diameter at ED was −0.61, whereas the correlation coefficient for ES was −0.26. Correlation coefficients for the CC dimension were 0.33 and 0.02 for ED
and ES, respectively. The correlation coefficient between each mitral annular geometric measure and mitral regurgitant volume per minute were all <0.5 or >−0.5 at both ED and ES. The correlation coefficient between the change in mitral regurgitant volume per minute and PL mitral regurgitant volume per minute was 0.71.

Effects of β-Blocker Treatment on Annular Dynamics

Figure 5 graphically depicts the effect of β-blockade on dynamic changes in annular dimensions throughout the cardiac cycle. SL is increased and CC is decreased for all time points for BB compared with PL (Figure 5A), which resulted in an overall decrease in eccentricity (CC/SL) for all cardiac phases (Figure 5B). Mitral annular height (Figure 5C), perimeter (Figure 5D), and area (Figure 5D) are decreased in BB compared with PL for all cardiac phases, but these differences were not statistically significant. A movie file depicting the mitral annular motion derived from the acquired data is available in the online supplement.

Discussion

In this study of asymptomatic or mildly symptomatic patients with moderate-to-severe primary MR of a myxomatous origin, changes in mitral annular dimensions and dynamics with β-blockers were evaluated from cardiac MRI images using a novel nonrigid registration automatic point-tracking procedure and a computer model of the annulus. Short-term treatment with β-blockers reduced or preserved all mitral annular dimensions, except SL at ES. Increases in mitral annular dimensions may result in failure of the MV leaflets to coapt, completely leading to worsening of MR. Therefore, treatment with a β-blocker may preserve or reduce mitral annular dimensions, and this may improve long-term outcomes of patients with chronic moderate and severe MR.4

β-Blocker Treatment Effects on Annular Geometry

In this same patient cohort, Stewart et al6 showed that β-blocker treatment significantly increased LVEDV and LVESV, a finding that is corroborated by Nemoto et al9 in a canine model of MR, which also included administration of angiotensin-converting enzyme inhibitors. However, mitral annular dimensions in these patients remained the same or decreased, except SL at ES, with short-term β-blocker treatment. The absence of significant increases in CC, annular perimeter, annular area, and eccentricity on β-blocker treatment may indicate a favorable long-term result for these patients.

Chronic ischemic MR is characterized by increases in the SL dimension. In contrast, in “pure” MR from a surgically created hole on the posterior MV leaflet, the primary change was increase in the CC dimension.10 Increased annular flattening also has been associated with increased MR. However, Nguyen et al10 found no change in saddle-shaped geometry as measured by annular height in their pure MR model. In the current study, the decrease in CC with no change in annular height is consistent with reversing or preventing the pathological changes seen in the pure MR model. β-blockers, therefore, may ameliorate or limit adverse remodeling of the annulus, which may be expected from volume overload as a consequence of MR alone.

In a canine model of chronic MR, Young et al11 used MRI to observe that the predominant mode of ventricular geometric remodeling was a shift of the septal wall away from the LV centroid into the right ventricle. Hence, increases in LVEDV in chronic MR lead to SL ventricular dilation. This predominant SL shift of the LV geometry may be exacerbated by β-blockers, which increase LVEDV and, by coupling to the mitral annulus, result in SL annular dilation. Therefore, change in LV volumes may have a greater impact on the SL dimension compared with other annular dimensions.
The increase in LVEDV and LVESV in patients treated with β-blockers in this study has been observed by others and is consistent with β-blockade use. The increases in SL at ES may arise from the observed increase in LV ESV but may not be sufficient to cause deleterious mitral annular remodeling because mitral annular perimeter decreased, mitral annular area was unchanged, and MR per minute decreased. However, further studies are needed to determine whether these short-term effects are maintained with long-term β-blocker treatment.

Another explanation for the increase in SL dimension could be differential effect of β-blockers on the fibrous and muscular annulus. The chronotropic and inotropic effects of β-blockers should increase the muscular annular length with concomitant increases in the LVEDV but may have a limited effect on the fibrous annulus, thereby tethering any potential increases in CC. Because the mitral annular perimeter is unchanged at ED and decreases at ES, the CC dimension is constrained to shorten while the SL dimension increases, leading to a significant decrease in annular eccentricity. Changes in mitral annular SL dimension at the annular level as a consequence of β-blocker treatment were moderately positively correlated with SL dimensional changes of the LV at ED, but changes in SL at ES and changes in CC and ED and ES were not correlated. Decreases in mitral regurgitant volume per minute do not likely occur as a consequence of changes in mitral annular geometry but, rather, as a consequence of inotropic and chronotropic effects. Lastly, a correlation was not established between mitral annular geometry and mitral regurgitant volume per minute. Note that patients with greater regurgitant volume per minute while on PL exhibited greater decreases in mitral regurgitant volume per minute when on BB. Therefore, decreases in mitral regurgitant volume per minute likely occur as a consequence of inotropic and chronotropic effects rather than of remodeling of the mitral annulus and appear to have a larger effect on patients with greater mitral regurgitant volumes per minute.

Our findings indicate that decreases in eccentricity (CC/SL) may be the most sensitive indicator of changes to mitral annular geometry because of the consistent decrease at both ED and ES. Note that Mahmood et al used 3D echocardiography to measure changes in mitral annular circularity index (equivalent to the inverse of the annular eccentricity reported herein) as a consequence of valve repair. From their results, we can ascertain that mitral annular eccentricity increases from 1.0 to 1.2 in myxomatous MV disease after repair with a Carpentier-Edwards physioannuloplasty ring. Therefore, the β-blocker-induced changes in eccentricity are about half those induced by a surgical repair. A correlation between changes in eccentricity and mitral regurgitant volume per minute, however, could not be established. The benefit, if any, of a decrease in eccentricity to the patient remains to be established.

Mitrval annular eccentricity values derived from the work of Nguyen et al in a chronic nonischemic MR sheep model increased at both ED and ES compared with controls. Hence, increases in eccentricity are associated with deleterious mitral annular remodeling. In our patient cohort, β-blockers conferred a decrease in eccentricity at both ED and ES, which suggests a therapeutic benefit to the patients.

Currently, there are no published reports on how medical treatment with β-blockers affects annular height measurements in humans. A decrease in annular height generally is associated with annular flattening, and flattening perpetuates MR. In the present study, annular height did not change significantly with short-term β-blocker treatment, but further studies are needed to evaluate longer-term effects.

**β-Blocker Treatment Effects on Annular Dynamics**

Using custom nonrigid registration automatic feature tracking software, we computed annular dimensions throughout the cardiac cycle from expertly selected seed points at ED. As shown in Figure 5, the annular changes during all time points in the cardiac cycle were consistent with the quantitative analysis performed at ED and ES (Table). In general, CC dimensions and annular eccentricity, height, perimeter, and area significantly decreased or remained the same at each point in the cardiac cycle. The annular SL dimension was observed to increase. The mean curves in BB-treated patients for each measure of annular dynamics remain consistently below the respective curves for the PL-treated patients, whereas the dynamic measures of SL were consistently increased on BB compared with PL. At no point in the cardiac cycle do the mean curves cross for any measure.

**Quantitative Image Analysis**

Image quality was suitable for automatic tracking of mitral annular points using custom nonrigid registration software. The software reduced the time spent quantitatively analyzing images by significantly reducing the need for user input while maintaining sufficient accuracy for quantitative comparisons. On average, the difference between mitral annular points chosen by an expert and those defined by the tracking software was <0.1 mm, thereby resulting in subpixel agreement. The automatic tracking software does not appear to significantly bias the location of the MV annulus when compared with expertly chosen points. Furthermore, the coefficients of variation for intra- and interobserver comparisons were low, except for annular height.

The recent advent of 3D echocardiography makes available another means for studying the MV; both transesophageal and transthoracic echocardiography looks promising. The MRI method reported herein for acquiring quantitative measures of mitral annular dimensions and dynamics, however, has the advantage of automated frame-to-frame point tracking, higher temporal resolution, and no required transesophageal probe compared with 3D echocardiography.

**Limitations**

This study evaluated the effects of 2 weeks of treatment with β-blockers on the mitral annulus, but LV remodeling usually occurs over several months. Therefore, longer-term studies are needed to confirm whether the observed effects of β-blocker treatment on mitral annular dimensions persist over time. In addition the MV annulus may remodel with a different time course and to a different degree than the ventricular myocardium. Furthermore, the patient’s response...
to β-blockers may be different based on the severity or etiology of MR. This study, however, is too small to allow reliable subgroup analysis. Long-term studies also are needed to determine the clinical significance of the observed changes in mitral annular geometry and their influence on long-term clinical outcomes. Lastly, examining mitral annular dimensions and dynamics subsequent to the cessation of the β-blocker regimen would confirm whether the measures returned to baseline.

Conclusions
Short-term β-blocker treatment in patients with moderate-to-severe MR reduced or preserved all mitral annular dimensions except SL at ES, even though LVEDV and LVESV increased. This favorable effect of β-blockade on mitral annular dimensions, if maintained with long-term treatment, combined with negative inotropic and chronotropic effects may reduce the progression of chronic MR.

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Disclosures
None.

References

CLINICAL PERSPECTIVE
Primary mitral regurgitation (MR), which usually is caused by myxomatous degeneration of the mitral valve (MV) leaflets, leads to a progressive increase in left ventricular (LV) volume. Eventually, this may result in LV dysfunction and heart failure. In patients with myxomatous MV disease, it has been shown previously that β-blockers reduced LV work and mitral regurgitant volume per minute, but the impact of β-blockers on MV annular dimensions and dynamics is uncertain. Twenty-five patients with moderate-to-severe degenerative MR and normal LV systolic function were studied in a double-blind crossover experiment using a β1-selective adrenergic blocker and placebo administered for 14±3 days. Cardiac MRI images were acquired after each treatment period, and mitral annular dimensions were quantified with semiautomated soft-tissue tracking software. Despite significant increases in LV end-diastolic and end-systolic volumes, short-term β-blocker treatment of patients with moderate-to-severe MR reduced or preserved the majority of mitral annular dimensions. This favorable effect of β-blockade on mitral annular dimensions, if maintained with long-term treatment, combined with negative inotropic and chronotropic effects may reduce the progression of chronic MR.
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SUPPLEMENTAL MATERIAL

Movie Legend: Movie of the mitral annulur model derived from automatic point tracking of manually selected annular points at end diastole. Each marker represents a point on the annulus that was visible in a long-axis magnetic resonance image (red – saddle horn, blue – anterior commisure, green – posterior commisure, orange – cantle).