Dobutamine-Induced Improvement in Inferior Myocardial Contractile Function Predicts Reduction in Functional Mitral Regurgitation

A Study Using Tissue Doppler Strain Rate Imaging

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Background—Left ventricular (LV) remodeling can increase tethering force to mitral valve and functional mitral regurgitation (FMR). Because the relationship between FMR and regional myocardial function has not been quantitatively evaluated, we conducted a quantitative investigation of this association.

Methods and Results—The effective regurgitant orifice (ERO) of FMR in 51 patients with depressed LV ejection fraction (32±9%) secondary to ischemic or nonischemic cardiomyopathy was compared with mitral deformation (valve and annulus), global LV remodeling (volume indices, function, and sphericity), and regional myocardial contractile function, as assessed by longitudinal peak systolic strain rate (Ssr) in LV anterior, anteroseptal, inferoseptal, inferior, inferolateral, and anterolateral segments at rest. Low-dose dobutamine (10 µg/kg per minute)-induced changes in ERO were compared with changes in the variables. Multivariable analysis identified the predictors of ERO at rest as mitral valvular tenting (β=0.062; P<0.001), Ssr in the inferior segment (inferior Ssr) (β=−0.178; P<0.001), and LV sphericity (β=0.414; P=0.001) and the predictors of valvular tenting at rest as inferior Ssr (β=−1.680; P<0.001), LV end-systolic volume index (β=0.022; P=0.001), and LV sphericity (β=3.886; P=0.012). Furthermore, dobutamine-induced reduction in ERO was predicted by reduction in valvular tenting (β=0.087; P<0.001) and increase in inferior Ssr (β=−0.82; P<0.001), and dobutamine-induced reduction in valvular tenting was predicted by increase in inferior Ssr (β=−0.86; P<0.001).

Conclusions—Inferior regional myocardial dysfunction was quantitatively associated with mitral valvular tenting and FMR. Moreover, improvement with dobutamine of inferior myocardial contractile function attenuated valvular tenting and FMR. Inferior myocardial contractile function can affect the configuration of the mitral apparatus and predict FMR severity. (Circ Cardiovasc Imaging. 2010;3:638-646.)

Key Words: cardiomyopathy ■ echocardiography ■ mitral valve ■ regurgitation

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unctional mitral regurgitation (FMR) is a common complication of ischemic and nonischemic dilated cardiomyopathy and adversely affects the patient’s prognosis.1,2 Left ventricular (LV) dilatation,3,4 sphericization,4 local rather than global LV remodeling,5–7 and global LV dysfunction8 leading to geometric changes in the mitral apparatus have been proposed as causes of FMR. The main cause of FMR is augmented leaflet tethering by apical displacement of the papillary muscle (PM) because of LV remodeling.3–8 In the presence of adjacent LV wall remodeling, regional LV dysfunction where PMs insert in can potentially increase leaflet tethering and FMR. However, clarification of the quantitative evaluation of the relationship between FMR and regional myocardial function has not been satisfactory. It has been shown that dobutamine can reduce FMR volume.9 However, the degree of reduction in FMR is different for each patient, and the beneficial effects of dobutamine have not been evaluated.

Clinical Perspective on p 646

Recently, the introduction of myocardial velocity measurements and the development of the strain rate (SR) imaging technique10 have made quantitative assessment of regional myocardial function possible. Thus, the purpose of this study was to investigate whether regional myocardial function as assessed by SR imaging is associated with FMR at rest and

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whether improvement in regional contraction with dobutamine causes reduction in FMR.

**Methods**

**Study Population and Protocol**

Fifty-four consecutive patients with ischemic cardiomyopathy (ICM) or non-ICM, depressed LV ejection fraction (EF) (<50%), and at least mild FMR were eligible for recruitment into the study. Exclusion criteria were the presence of recent myocardial infarction (<6 weeks); MR caused by intrinsic mitral valvular lesions; and other cardiac diseases, such as congenital defects, aortic valve disease, or pericardial disease. Of these patients, 3 were excluded because of inadequate echocardiographic image quality, so 51 patients (35 men and 16 women aged 67 ± 11 years) were enrolled (Table 1). The diagnosis given for 29 patients was ICM, which was defined as the presence of coronary artery disease (≥75% stenosis) and/or prior coronary revascularization, with double- and triple-vessel disease identified in 6 and 23 patients, respectively. Although 22 patients had non-ICM, all showed angiographically normal coronary arteries, and there was no evidence of myocardial infarction either in history or on ECGs. All patients gave written informed consent.

**Echocardiographic Examination**

Echocardiographic examination was performed using SSH 770A and a 3-MHz transducer (Toshiba Medical Systems; Tokyo, Japan) at rest and during dobutamine infusion (10 μg/kg per minute). Electrocardiography was performed throughout the study, and blood pressure and heart rate were obtained at 1-minute intervals. LV end-diastolic volume, end-systolic volume, and EF were obtained with the modified biplane Simpson’s method. LV sphericity was calculated as the LV short-axis/long-axis ratio in the end-systolic apical 4-chamber view (Figure 1). LV volumes and sphericity index were considered as global LV remodeling variables. The mitral annulus (MA) was identified as the leaflet hinge point. The MA area was obtained by determining the annular dimensions in apical 2- and 4-chamber views followed by calculation of the MA area as $d_1 \times d_2 \times \pi/4$ (Figure 1), where $d$ is the mitral annular dimension. Tenting area was measured as the area enclosed between the annular plane and leaflets in the late-systolic parasternal long-axis view (Figure 1).5 Displacement of mitral coaptation (coaptation height) toward the LV apex was measured by determining the distance between leaflet coaptation and the MA plane in the apical 4-chamber view (Figure 1).11 The MA area, tenting area, and coaptation height were adopted as mitral deformational variables.

To assess the severity of MR, FMR volume and ERO were calculated with the volumetric method. FMR volume was calculated as the difference between mitral filling and aortic ejection volume and ERO as FMR volume divided by the time-velocity integral of FMR flow.

**Tissue Doppler Imaging and SR Measurements**

Tissue Doppler images in apical long-axis, 2- and 4-chamber views were recorded at rest and during dobutamine infusion. Digital data were transferred to dedicated software (apliQ; Toshiba Medical Systems) for subsequent offline analysis, and the SR could be obtained by calculating the velocity gradient because SR equals the spatial gradient of velocity.10 Regions of interest were 4 × 4 mm² and placed on the anterior, anteroseptal, inferoseptal, inferior, inferolateral, and anterolateral segments at midventricular level in the apical views (Figure 2). These regions of interest were then tracked manually frame by frame to keep each of them in the same midmyocardial position during the entire cardiac cycle.

LV longitudinal peak systolic SR (Ssr), defined as the maximal negative SR during systole, was measured in each segment (Figure 2).

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**Table 1. Demographic and Clinical Characteristics of Study Population (n=51)**

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>67±11</td>
</tr>
<tr>
<td>Male/female sex</td>
<td>35/16</td>
</tr>
<tr>
<td>NYHA functional class</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>21</td>
</tr>
<tr>
<td>III</td>
<td>30</td>
</tr>
<tr>
<td>Risk factors and concomitant diseases</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>21 (41)</td>
</tr>
<tr>
<td>Systemic hypertension</td>
<td>35 (69)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>26 (51)</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>29 (57)</td>
</tr>
<tr>
<td>Anterior</td>
<td>17 (33)</td>
</tr>
<tr>
<td>Lateral</td>
<td>10 (20)</td>
</tr>
<tr>
<td>Inferoposterior</td>
<td>15 (29)</td>
</tr>
<tr>
<td>Nonischemic global LV dysfunction</td>
<td>22 (43)</td>
</tr>
<tr>
<td>Revascularization</td>
<td>22 (43)</td>
</tr>
<tr>
<td>Post percutaneous coronary intervention</td>
<td>14 (27)</td>
</tr>
<tr>
<td>Post coronary artery bypass graft</td>
<td>11 (22)</td>
</tr>
<tr>
<td>Drugs</td>
<td></td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>11 (22)</td>
</tr>
<tr>
<td>Angiotensin receptor blockers</td>
<td>34 (67)</td>
</tr>
<tr>
<td>β-blockers</td>
<td>36 (71)</td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>44 (86)</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>32 (63)</td>
</tr>
</tbody>
</table>

Data are presented as n, mean±SD, or n (%). ACE indicates angiotensin-converting enzyme; NYHA, New York Heart Association.
2). All measurements were performed on serviceable tracings, with the final value representing the absolute averaged Ssr of 3 cardiac cycles per segment.

Reproducibility of SR Measurements
In 60 segments randomly selected from the total of 612 segments, interobserver and intraobserver reproducibility of the measurement of Ssr was evaluated by 2 independent observers. To assess the interobserver reproducibility, selected segments were analyzed by the second observer blinded to the values obtained by the first observer. To assess the intraobserver reproducibility, selected segments were analyzed on 2 consecutive days by an observer blinded to the results of the previous measurements. Interobserver and intraobserver reproducibility was evaluated by the intraclass correlation coefficient.

Statistical Analysis
All data are expressed as mean±SD. Group comparisons between at rest and with dobutamine were performed using paired t test. Group comparisons between ICM and non-ICM were performed using unpaired Student t test. Differences among Ssrs of the 6 segments were tested by repeated-measures ANOVA. Individual linear regression analysis was initially applied to study the relation between ERO at rest and echocardiographic variables. To determine independent predictors of the degree of FMR, multiple linear regression analysis with stepwise selection was performed. Because of the multicollinearity between tenting area and regional myocardial function, we decided to choose the systolic variable in the multivariable linear regression model because FMR appears during the systolic phase. We specified the entry and retention P values in stepwise selection as P<0.05. A similar multivariable analysis was performed with reductions in ERO. A P<0.05 was considered statistically significant. SPSS for Windows release 13.0 (SPSS Inc; Chicago, Ill) and R version 2.92 (R Foundation for Statistical Computing; Vienna, Austria) were used for statistical analyses.

The authors had full access to the data and take full responsibility for their integrity. All authors have read and agreed to the manuscript as written.

Results
Baseline Characteristics
The study included 51 patients with severe LV dysfunction (EF, 32±9%), high LV sphericity (sphericity index, 0.63±0.11), and moderate FMR (ERO, 0.28±0.12 cm²) at rest (Table 2). There was no difference between ICM and non-ICM at rest in terms of hemodynamics, LV geometry, LV global function, FMR, mitral valvular deformation, or Ssr in any of the segments (Table 3).

SR Imaging Analysis
Quantitative evaluation of myocardial SR could be performed in 608 of the 612 segments representing the sum of the 6 segments of LV in all 51 patients at rest and during dobutamine infusion. There are no data in 4 segments because the lung interrupted the creation of ultrasound images of the LV myocardium. Although the Ssr values at rest showed a wide range (0.23 to 2.64/s), the averaged Ssr at rest in total patients
for any 1 segment did not significantly differ among the 6 segments ($P=0.22$).

### Predictors of the Degree of FMR and Tenting Area at Rest

ERO at rest was associated with LV volume indices, EF, sphericity index, tenting area, coaptation height, MA areas, and Ssr in the inferior and anterolateral segments but not with Ssr in the anterior, anteroseptal, inferoseptal, or inferolateral segments (Figure 3, Table 4). Multivariable linear regression analysis demonstrated that the predictors of ERO at rest were tenting area ($\beta=0.062; P<0.001$), Ssr in the inferior segment (inferior Ssr) ($\beta=-0.178; P<0.001$), and LV sphericity index ($\beta=0.414; P=0.001$) (Table 5).

Tenting area was associated with LV volume indices, EF, sphericity index, coaptation height, MA areas, Ssr, and anterior Ssr. Multivariable analysis revealed that inferior Ssr ($\beta=-1.680; P=0.001$), LV end-systolic volume index ($\beta=0.022; P=0.001$), and LV sphericity index ($\beta=3.886; P=0.012$) were the independent predictors of tenting area.

Comparison of patients with ICM and non-ICM by means of individual analysis showed similar regressions between ERO and LV volume indices, sphericity index, tenting area, coaptation height, MA areas, and inferior Ssr. Multivariable analysis of ICM identified tenting area and inferior Ssr as the independent predictors of ERO, whereas those for non-ICM were tenting area, inferior Ssr, and LV sphericity index with marginal significance.

### Dobutamine-Induced Changes in FMR and Tenting Area

Dobutamine increased heart rate, blood pressure, LV EF, and Ssr in all segments, and reduced LV volume indices, sphericity index, MR volume, ERO, tenting area, coaptation height, and MA areas (Figure 4, Table 2). The reduction in ERO caused by dobutamine was associated with reductions in LV sphericity index, tenting area, coaptation height, MA areas, and increases in inferior Ssr and anterolateral Ssr (Figure 5, Table 6).

Multivariable analysis showed that the reduction in tenting area ($\beta=0.087; P<0.001$) and the increase in inferior Ssr ($\beta=-0.82; P<0.001$) were the predictors of the reduction in ERO (Table 7). Moreover, multivariable analysis revealed that the increase in inferior Ssr ($\beta=-0.860; P<0.001$) was the only independent predictor of the reduction in tenting area.
Reproducibility

The intraclass correlation coefficient for interobserver reproducibility was 0.883 (95% CI, 0.714 to 0.944). The intraclass correlation coefficient for intraobserver reproducibility was 0.957 (95% CI, 0.929 to 0.974).

Discussion

The findings of our study demonstrated that inferior myocardial contractile function played a major role in the configuration of the mitral apparatus associated with FMR. To the best of our knowledge, this study is the first to provide quantitative evidence of the association between inferior myocardial function and the severity of FMR as a result of valvular tenting and the dobutamine-induced reduction in FMR caused by improved inferior myocardial function.

The mechanism of FMR consists of (1) apical tethering of mitral leaflets due to the outward displacement of the PM by local LV remodeling or global LV remodeling and dilatation, which is accompanied by restricted systolic leaflet motion, and (2) MA dilatation secondary to LV enlargement, which causes incomplete mitral valve coaptation associated with normal leaflet motion.3–8

Tenting Area and FMR

Mitrail tenting area is a simple variable that represents valvular configuration caused by changes in LV geometry and by myocardial dysfunction and is 1 of the predictors of FMR severity.5,7 Global LV remodeling, dysfunction, and sphericization aggravate tethering of the mitral valve and cause displacement of the valvular coaptation point toward the apex.3–8 This apical displacement of PMs further reduces the contact between mitral leaflets and compromises valve competence, which causes FMR.

In this study, we also found that excess tenting was associated with a larger ERO at rest in patients with either ICM or non-ICM. Dobutamine decreased FMR with decreased tenting area; moreover, the diminished tenting following dobutamine infusion correlated positively with the reduction in FMR. Although it has been shown that exercise increased FMR7,12,13 with increased tenting area and that an exercise-induced increase in tenting also correlated positively with an exercise-induced increase in FMR,7,12 the changes in FMR resulting from exercise and dobutamine were different, whereas the positive correlations between tenting and FMR and by myocardial dysfunction and is 1 of the predictors of FMR severity.5,7 Global LV remodeling, dysfunction, and sphericization aggravate tethering of the mitral valve and cause displacement of the valvular coaptation point toward the apex.3–8 This apical displacement of PMs further reduces the contact between mitral leaflets and compromises valve competence, which causes FMR.

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Table 4. Results of Individual Linear Regression Analysis at Rest

<table>
<thead>
<tr>
<th>Dependent Variables</th>
<th>β</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV geometry and function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDVI, mL/m²</td>
<td>0.0017</td>
<td>0.00065 to 0.0028</td>
<td>0.002</td>
</tr>
<tr>
<td>ESVI, mL/m²</td>
<td>0.0019</td>
<td>0.00083 to 0.0030</td>
<td>0.001</td>
</tr>
<tr>
<td>EF, %</td>
<td>−0.0052</td>
<td>−0.0086 to −0.0018</td>
<td>0.003</td>
</tr>
<tr>
<td>Sphericity index</td>
<td>0.508</td>
<td>0.224 to 0.792</td>
<td>0.001</td>
</tr>
<tr>
<td>Mitral valvular deformation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tenting area, cm²</td>
<td>0.062</td>
<td>0.048 to 0.076</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Coaptation height, cm</td>
<td>0.027</td>
<td>0.017 to 0.037</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic MA area, cm²</td>
<td>0.044</td>
<td>0.019 to 0.070</td>
<td>0.001</td>
</tr>
<tr>
<td>Systolic MA area, cm²</td>
<td>0.054</td>
<td>0.028 to 0.079</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peak Ssr, 1/s</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior</td>
<td>−0.0046</td>
<td>−0.084 to 0.075</td>
<td>0.91</td>
</tr>
<tr>
<td>Anteroseptal</td>
<td>0.0051</td>
<td>−0.071 to 0.081</td>
<td>0.89</td>
</tr>
<tr>
<td>Inferoseptal</td>
<td>−0.0083</td>
<td>−0.090 to 0.073</td>
<td>0.84</td>
</tr>
<tr>
<td>Inferior</td>
<td>−0.203</td>
<td>−0.292 to −0.114</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Inferolateral</td>
<td>−0.028</td>
<td>−0.103 to 0.046</td>
<td>0.45</td>
</tr>
<tr>
<td>Anterolateral</td>
<td>−0.074</td>
<td>−0.141 to −0.0062</td>
<td>0.033</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 2.

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Table 5. Predictors of ERO at Rest

<table>
<thead>
<tr>
<th>Model using variables of mitral deformation*</th>
<th>β</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenting area, cm²</td>
<td>0.062</td>
<td>0.048 to 0.076</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Model using variables of LV remodeling and regional myocardial function†

| LV sphericity index                  | 0.414 | 0.167 to 0.660 | 0.001 |
| Ssr in inferior segment, 1/s         | −0.178 | −0.261 to −0.096 | <0.001 |

*Adjusted $\hat{R}^2=0.608$
†Adjusted $\hat{R}^2=0.410$
were shown to apply to both exercise-induced and dobutamine-induced changes.

The associations in our study between tenting and global LV remodeling were stronger than those between ERO and global LV remodeling. The reason for this finding may be that FMR is related to 2 different patterns of mitral valve leaflet tethering (symmetrical or asymmetrical), which essentially are determined by the type of LV remodeling. The common denominator of these 2 patterns is the presence of severe posterior leaflet restriction combined with either severe anterior leaflet restriction (symmetrical tethering) or mild anterior leaflet restriction (asymmetrical tethering). Some cases in our study showed symmetrical tethering associated with mild or moderate FMR with severe tenting, suggesting that a mitral valve with symmetrical tethering attains better coaptation than does a mitral valve with asymmetrical tethering.

Regional Myocardial Function and FMR

The incidence of FMR in patients with inferior myocardial infarction is higher than in those with anterior myocardial infarction because FMR is associated with more-severe geometric changes in the mitral valve apparatus and with greater displacement of posterior PM caused by localized inferior basal LV remodeling. Thus, it can be expected that not only inferior remodeling, but also inferior myocardial dysfunction can cause FMR.

Table 7. Predictors of Decrease in ERO

<table>
<thead>
<tr>
<th>Model using variables of mitral deformation*</th>
<th>( \Delta )</th>
<th>95% CI</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \Delta ) Tenting area, cm(^2)</td>
<td>0.087</td>
<td>0.072 to 0.102</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Model using variables of LV remodeling and regional myocardial function†</th>
<th>( \Delta )</th>
<th>95% CI</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \Delta ) Ssr in inferior segment, 1/s</td>
<td>-0.082</td>
<td>-0.114 to -0.051</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Adjusted \( R^2 = 0.735 \).
†Adjusted \( R^2 = 0.351 \).
Previous investigators have reported that FMR develops in association with poor regional systolic function of the LV segments overlying the anterior and posterior PMs.\textsuperscript{16} Furthermore, the predictors of tenting are the average wall motion score indices for 8 segments attached to the PMs,\textsuperscript{3} and the reduction in FMR correlates with the decrease in the average wall motion score index for those segments.\textsuperscript{17} These findings agree with ours, although the wall motion score index reported previously was semiquantitative, and the regions of interest included not only the inferior site, but also the anterolateral sites. Our study used SR imaging to demonstrate quantitatively the association between regional myocardial function and severity of FMR. Furthermore, it has been found that the posterior PM tethering distance (ie, between the posterior PM tip and intervalvular fibrosa [contralateral anterior annulus]) is the main determinant of FMR and/or mitral tenting.\textsuperscript{5,7,15} This finding suggests the importance of inferior myocardial function because the inferior segment constitutes the posterior PM insertion site.

Inferior myocardial dysfunction and posterior PM dysfunction are contradictory findings for FMR, although they frequently coexist in patients with FMR. Inferior myocardial dysfunction, which increases the distance from the inferior myocardium to intervalvular fibrosa, augments FMR with increased PM tethering distance. On the other hand, PM dysfunction, which reduces its longitudinal contraction to induce leaflet tethering, attenuates FMR\textsuperscript{18} with diminished PM tethering distance. Several investigators reported that local rather than global LV remodeling increases tethering of the mitral valve and FMR.\textsuperscript{5,7,15} In the present study, we found that inferior myocardial dysfunction was associated with excess tenting and FMR. The inferior segmental displacement during systole, which resulted from less movement of the inferior segment toward the intervalvular fibrosa, pulled the stay cords and posterior PM and then tethered the body of the leaflet, leading to incomplete closure of the mitral valve. The similar mechanism also may exist on the anterolateral site. Dobutamine improved myocardial contractility and augmented the movement of the inferior segment toward the fibrosa so that tethering of the mitral valve and FMR were reduced. The findings of dobutamine-induced reduction in FMR supported the relationship between the inferior myocardial dysfunction and FMR.

Comparison of Patients With ICM and Non-ICM

LV sphericity was 1 of the determinants of FMR in non-ICM but not in ICM in this study. Agricola et al\textsuperscript{14} reported that the stenosis of the left descending artery was involved in all patients in a symmetrical tethering group, whereas the stenosis of the right coronary artery was significantly more frequent in the asymmetrical group; moreover, LV in the symmetrical tethering group was significantly more spherical than that in the asymmetrical one. Their results indicate that ICM with anterior infarction has high LV sphericity with global LV remodeling, whereas ICM with interoposterior infarction has less LV sphericity than those with anterior infarction. In our study, 15 of the 29 patients with ICM had interoposterior infarction, although all the patients with ICM had multivessel disease. Relative high incidence of interoposterior infarction would be the reason why LV sphericity did not determine FMR severity in ICM in our study. Nagasaki et al\textsuperscript{19} also demonstrated that LV sphericity mainly determined the MR severity of non-ICM but not ICM. Kwan et al\textsuperscript{20} reported that the pattern of mitral valve deformation from the medial to the lateral side was asymmetrical in ICM with interoposterior infarction, whereas it was symmetrical in non-ICM. LV sphericity also would be the main cause of these differences of mitral deformation.

Inferior myocardial contractile function and valvular tenting were the main predictors in FMR in ICM and non-ICM, respectively, in our study. Moreover, the changes in inferior myocardial function and tenting were the main predictors in reduction in FMR with dobutamine. These results indicate that the mechanism of FMR and inferior contractile function operating through the mitral apparatus is constructed in the presence of ICM and non-ICM. A previous study demonstrated that tenting area was the strongest predictor of FMR severity in both ICM and non-ICM; thus, these findings agree well with those of the present study.

There would be no significant difference in dobutamine effects on the regional function between ICM and non-ICM in this study because the low-dose dobutamine used in this study would not lead to ischemic phenomenon, even if there was a coronary stenosis. Indeed, there was no significant difference in dobutamine effect between ICM and non-ICM on each Ssr in 6 segments.

Comparing Exercise and Dobutamine Stress

Echocardiography in FMR

The purpose of a dobutamine stress test may be different from an exercise stress test. Dobutamine detects myocardial contractile reserve\textsuperscript{21,22}, on the other hand, exercise predicts global cardiac capacity with increased LV preload and afterload.\textsuperscript{11}

It has been shown that exercise stress increases FMR\textsuperscript{7,12,13} because it (1) increases the LV preload due to increased venous return, (2) increases systemic vascular resistance in conjunction with the autonomic nervous system, (3) causes an increase in LV sphericity,\textsuperscript{12} and (4) dilates the MA.\textsuperscript{7,12} On the other hand, the cardiovascular effects of dobutamine are augmentation of contractility; thus, dobutamine decreases FMR because it (1) reduces the LV preload, (2) reduces systemic vascular resistance with its affinity for β2 receptor, (3) causes a decrease in LV sphericity, and (4) contracts the MA. The main reason why exercise and dobutamine stress have different effects on FMR would be the different changes in preload and afterload conditions. Nevertheless, further investigation is needed to clarify the different effect of load conditions on LV and MA function between exercise and dobutamine.

Exercise stress can predict morbidity or mortality in patients with LV dysfunction\textsuperscript{23} but cannot determine the myocardial contractile reserve. On the contrary, dobutamine stress can detect the myocardial contractile reserve.\textsuperscript{21,22} The importance of the present study was to evaluate the regional myocardial contractile reserve; therefore, we used the dobutamine stress test.
SR Imaging and Dobutamine Stress Echocardiography

Systolic SR is a noninvasive indicator of myocardial contractile function that is less affected by segmental tethering and translational motion and allows quantification of myocardial deformation within individual segments. In the presence of myocardial viability, dobutamine is able to concomitantly decrease MR volume. Previous studies have indicated that SR imaging accurately reflects regional contractility and viability both at rest and during dobutamine infusion. We therefore chose SR imaging as most suitable for evaluating regional myocardial contractile function in this study.

Clinical Implications

FMR adversely affects the prognosis of patients with ICM and non-ICM. In the present study, FMR was associated with inferior myocardial contractile function, and dobutamine-induced improvement in inferior myocardial function was associated with reduction in FMR. Meanwhile, dobutamine stress echocardiography can be used to assess LV contractile reserve, which is a significant determinant of improvement in cardiac function with medical treatment, including β-blocker therapy. Therefore, dobutamine-induced improvement in inferior myocardial function could predict reversed inferior function and reduction in FMR with medical treatment, and thus, dobutamine stress echocardiography could predict positive prognosis in patients with FMR, especially when assessing improvement in inferior function and FMR. Exercise stress, on the other hand, provides a negative prognosis with indication of worsened FMR and increased pulmonary hypertension. Furthermore, the results of the present study suggest that in patients with ICM, revascularization to the right coronary artery territory with a viable myocardium could potentially benefit patients by reversing myocardial function and reducing FMR.

Study Limitations

The present study has several limitations. First, for evaluation of FMR, we used ERO with the volumetric method rather than the proximal isovelocity surface area method because the geometry of the proximal isovelocity surface area in FMR is elongated, leading to underestimation of the ERO. Second, tenting variables in this study were measured on a single plane, which is not sufficient for assessing the relationship between valve geometry and LV regional function. Further investigation with 3D assessment of valve geometry is required in the future. Finally, tissue Doppler SR imaging has angle dependency. We could scan as parallel as possible to the regions of interest because the LV has high sphericity and mid-LV segments were nearly parallel to and in plane with the scan line.

Conclusions

We demonstrated with the tissue Doppler SR imaging method that inferior regional myocardial dysfunction was quantitatively associated with mitral valvular tenting and FMR. Improvement in inferior myocardial contractile function resulting from dobutamine infusion attenuated mitral valvular tenting and FMR. These results indicate that inferior myocardial contractile function affects configuration of the mitral apparatus and determines severity of FMR.

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Disclosures

None.

References

CLINICAL PERSPECTIVE

Left ventricular (LV) remodeling can increase tethering of the mitral valve and be associated with functional mitral regurgitation (FMR). However, the relationship between FMR and regional myocardial function has not been quantitatively evaluated. The aim of this study is to conduct a quantitative investigation of this association at rest and with dobutamine using longitudinal systolic strain rate (Ssr) derived from tissue Doppler echocardiography as regional myocardial function. The effective regurgitant orifice (ERO) of FMR in 51 patients with depressed LV ejection fraction was compared with mitral deformation, global LV remodeling, and Ssr in 6 mid-LV segments. Multivariable analysis identified the predictors of ERO at rest as mitral valvular tenting, Ssr in the inferior segment (inferior Ssr), and LV sphericity and the predictors of valvular tenting at rest as inferior Ssr, LV end-systolic volume index, and LV sphericity. Furthermore, dobutamine-induced reduction in ERO was predicted by a reduction in valvular tenting and an increase in inferior Ssr, and dobutamine-induced reduction in valvular tenting was predicted by an increase in inferior Ssr. The results of this study suggest that inferior myocardial contractile function affects the configuration of mitral apparatus and predicts FMR severity. Dobutamine-induced improvement in myocardial function is known to predict improved function with medical treatment, and thus, dobutamine stress echocardiography could be used to predict improvement in FMR with appropriate treatment especially by assessing inferior contractile reserve. Furthermore, this test could be useful in predicting whether revascularization of viable myocardium in the inferior distribution might be associated with improvement in FMR.
Dobutamine-Induced Improvement in Inferior Myocardial Contractile Function Predicts Reduction in Functional Mitral Regurgitation: A Study Using Tissue Doppler Strain Rate Imaging

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