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# Acute Versus Chronic Ischemic Mitral Regurgitation

## An Echocardiographic Study of Anatomy and Physiology

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**BACKGROUND:** Little is known on the mechanism of acute ischemic mitral regurgitation (IMR) caused by sudden-onset left ventricular dysfunction in acute myocardial infarction (MI). We sought to investigate the mitral valve (MV) complex geometry in acute IMR in comparison with chronic IMR by 2-dimensional and 3-dimensional transthoracic echocardiography.

**METHODS AND RESULTS:** Forty-four first-onset acute MI and 36 previous MI with ≥moderate IMR were examined by 2-dimensional/3-dimensional transthoracic echocardiography. MV morphology was quantitatively analyzed and compared between the 2 groups. Left ventricular end-diastolic volume and left ventricular end-systolic volume were significantly smaller in acute IMR than in chronic IMR (40.8 [33.1–48.3] versus 88.8 [66.5–108.8] mL/m$^2$; $P$<0.001, 17.8 [17.0–30.1] versus 49.5 [34.2–73.7] mL/m$^2$; $P$<0.001). MV tenting volume and annular area were significantly smaller in acute IMR compared with chronic IMR (0.98 [0.66–1.68] versus 1.88 [1.16–2.65] cm$^3$/m$^2$; $P$=0.008, 5.17 [4.80–5.86] versus 5.81 [5.47–8.22] cm$^2$/m$^2$; $P$=0.008). Leaflet surface area was significantly smaller in acute IMR than in chronic IMR (5.78 [5.16–6.32] versus 7.56 [6.89–11.32] cm$^2$/m$^2$; $P$<0.001). The ratio of MV leaflet surface area and MV annular area was significantly smaller in acute IMR than in chronic IMR (1.08 [1.01–1.14] versus 1.28 [1.24–1.37]; $P$=0.001).

**CONCLUSIONS:** Sudden-onset left ventricular dysfunction in acute MI may cause loss of coaptation of the MV even with a relatively mild degree of valve tethering. Compared with previously studied chronic IMR, a smaller leaflet area without leaflet adaptation and a larger hemodynamic burden at the acute onset of MI could result in clinically significant IMR despite relatively small leaflet tethering.

**Key Words:** echocardiography ■ hemodynamic ■ mitral valve ■ myocardial infarction ■ prognosis



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## CLINICAL PERSPECTIVE

Ischemic mitral regurgitation (IMR) has been recognized as a clinically important complication after myocardial infarction that can worsen the long-term prognosis. IMR is highly dynamic, especially during the acute phase of ischemia over the course of emergency revascularization. The role of surgical repair or catheter intervention for MR is still controversial with limited and conflicting data based on various surgical strategies. Clarifying the mechanisms of IMR development from the early stage to the chronic stage after myocardial infarction is needed for the development of appropriate therapeutic strategies for the complex pathology. In the present study, we evaluated the 3-dimensional geometric characteristics in the mitral valve apparatus in acute IMR and found that acute IMR could occur with milder mitral valve tenting compared with chronic IMR. The present study provides new insights into the mechanism of acutely progressed IMR early after the onset of acute myocardial infarction. There are elements other than pathological PM geometry due to ventricular remodeling that contribute to the imbalance between tethering and closing forces, i.e. LV systolic pressure, contractility and annular remodeling. The results of the present study should be the first step in understanding the pathology of acute IMR in the clinical setting. Serial changes in the mitral valve complex geometry over the course of myocardial infarction should be investigated to reach a further understanding of the complex mechanisms of IMR.

Ischemic mitral regurgitation (IMR) has been recognized as an important complication after myocardial infarction (MI) and is known to worsen patients' prognoses even with a mild degree of MR.[1,2] The mitral valve (MV) tethering phenomenon caused by left ventricular (LV) remodeling after MI in the chronic clinical stage has been widely accepted by previous experimental and clinical studies as a mechanism of IMR. However, most previously published studies on the mechanism of IMR have been based on IMR in the subacute or chronic period of MI,[3–6] and little is known on the mechanism of acute IMR. We have recently investigated the course of IMR after first-onset acute MI (AMI)[2] and have reported that the degree of acute IMR can dramatically change after emergency revascularization. This was the first clinical study that evaluated the serial changes in IMR from the very acute phase of AMI, and we found that the existence of acute IMR before primary percutaneous coronary intervention (PCI) resulted in an adverse 30-day prognosis after AMI. Acute IMR secondary to sudden-onset MI may have unique mechanisms different from previously evaluated IMR in ischemic cardiomyopathy. The prognostic impact of surgical or catheter intervention of the secondary MR after MI is still controversial, and clarifying the mechanisms of IMR over the course of MI is an important clinical issue. In the present study, we quantitatively assessed the MV complex geometry using real-time transthoracic 3-dimensional (3D) echocardiography in patients with first-onset AMI with significant acute IMR, and compared the MV morphology with classical IMR caused by chronic LV and MV remodeling after MI, and then compared each acute and chronic IMR group with no-IMR controls.

## METHODS

The data, analytic methods, and study materials will not be made available to other researchers for purpose of reproducing the results or replicating the procedure.

### Study Patients

We prospectively enrolled 44 consecutive first AMI patients with significant IMR on their arrival at Miyazaki Medical Association Hospital Cardiovascular Center. AMI was defined as MI within 72 hours from the onset symptoms as per the Third Universal Definition of Myocardial Infarction.[7] Thirty-six previous MI patients with significant IMR who visited our echocardiographic laboratory for a routine check-up were consecutively recruited as the chronic IMR group. Significant MR was defined as ≥moderate MR at the time of echo examination. Twenty AMI without MR, 20 chronic stage post-MI (>1 year, LV ejection fraction <50%) without MR (post-MI without MR), and 14 non-MI normal were analyzed as controls to compare the mitral apparatus geometry with the acute IMR group and the chronic IMR group. Exclusion criteria were as follows: (1) the presence of organic MV or aortic valve diseases, (2) inadequate echocardiographic images, (3) mechanical complications of AMI or cardiac shock on arrival, and (4) atrial fibrillation or atrioventricular block at the time of echocardiography.

This study was performed in accordance with the institution review board and ethics committee of the Miyazaki Medical Association Hospital. All patients gave informed written consent.

### Echocardiographic Protocol

Each patient underwent standard 2D, Doppler, and real-time 3D echocardiography. For first AMI patients, echocardiographic exams were performed immediately after a patient's arrival at the emergency room as a protocolized patient care for acute coronary syndrome. Echocardiography was performed using IE33 and EPIQ (Philips Medical Systems, Bothell, WA), with an X-5 probe for 2D and real-time 3D images.

### Two-Dimensional Echocardiographic Study

Mitral regurgitation was evaluated by color Doppler echocardiography. The degree of MR was quantified by average

vena contracta width on apical 4-chamber and 2-chamber color Doppler images as per previous study. Average vena contracta width of ≥5 mm was defined as ≥moderate in this study.[2] Regurgitant volume was measured by proximal isovelocity surface area method or Doppler equation method. MV tenting height, MV tenting area, and annular diameter were measured in the parasternal long-axis view as per previously published articles[6,8] using TomTec-Arena (TomTec, Germany).

## Three-Dimensional Echocardiographic Study

Using a real-time 3D echocardiographic system, we obtained transthoracic volumetric images (full-volume mode) with the apical view for all subjects. The volumetric frame rate was 20 to 26 frames/s, with an imaging length of 14 to 18 cm. Before acquiring the full-volume image, we carefully adjusted the transducer position to have it located at the apex in biplane mode. All volumetric images were digitally stored on compact disc and transferred to a personal computer for offline analysis by QLAB (Philips Medical Systems, Bothell, WA) and REAL VIEW (YD Ltd, Nara, Japan).[9] The procedures for offline analysis by using REAL VIEW are described in Figure 1. As previously reported,[9,10] the 3D data were automatically cropped into 18 radial planes oriented 10° apart. The mitral annulus in each cropped plane was manually plotted, whereas the mitral leaflets were traced semiautomatically in each cropped plane. The tips of the papillary muscle (PM) were captured and marked on cropped planes. The total leaflet area was assessed at the onset of mitral leaflet closure. The mitral annular area was calculated at midsystole. The tenting volume was calculated as the volume enclosed between the estimated curved annular surface and mitral leaflets at midsystole. To observe the PM displacement, we measured the distance between the tips of the anterior or posterior PM and intervalvular fibrosa (the middle anterior part of the annulus) as the lateral or medial tethering length in midsystole. Leaflet length and coaptation length were measured by using QLAB with multiplanar reconstruction mode. The leaflet length at the middle site was measured on the optimal long-axis cut plane at diastole with multiplanar reconstruction mode. The middle site was determined as the center of the MV.

All these measurements and analysis were independently assessed by 2 experienced observers (S.N. and N.W.) who were blinded to clinical data.

## Statistical Analysis

Continuous variables were expressed as mean±SD or median and interquartile range where appropriate. Categorical variables were reported as numbers and frequency (%). Continuous parameters were checked for the normality of distribution using the Shapiro–Wilk test and compared using the unpaired *t* test or Wilcoxon rank-sum test with normal and non-normal distributions, respectively. AMI without MR, previous MI without MR, and non-MI normal group were compared as no-MR controls for each acute IMR and chronic IMR group. Comparisons were performed between the groups as follows: (1) acute IMR versus chronic IMR, (2) acute IMR versus AMI without MR, (3) acute IMR versus previous MI without MR, and (4) chronic IMR versus previous MI without MR, and then each acute IMR and chronic IMR group versus non-MI normal. Categorical data were compared using the likelihood-ratio $\chi^2$ test or Fisher exact test. A 2-sided *P* value <0.05 was considered to indicate statistical significance. All analyses were performed using IBM SPSS Statistics (version 22; IBM Corporation, Somers, NY). The association between the tenting area and the average vena contracta width or LV systolic dimension was investigated with the regression analysis. Spearman rank correlation coefficient was used to assess associations between 2 groups. For non-normally distributed variables entered into regression models, the assumption of normally distributed residuals was verified by quantile plots, and not violations were observed. Interobserver and intraobserver variabilities were assessed for 10 randomly selected exams. Interobserver variability was calculated as the absolute difference between the 2 readings, as a percent of their mean, and averaged over 10 exams. Intraobserver variability was calculated as the absolute difference between the first and second determinations (3-week interval) for a single observer, as a percent of their mean, and averaged over 10 exams.

# RESULTS

## Acute Versus Chronic IMR

Baseline patient characteristics and echocardiographic parameters are shown in Table 1. There were more male patients in the chronic IMR group compared with the acute IMR group. There were no significant differences in the culprit vessels. Systolic and diastolic blood pressure at the time of examinations were significantly higher in the acute IMR group than in the chronic IMR group (148±29 versus 124±33 mm Hg; *P*=0.009, 86±14 versus 66±12 mm Hg; *P*<0.001). There were no significant differences in heart rate between the 2 groups. LV systolic and diastolic diameter and volume were significantly smaller in the acute IMR group than in the chronic IMR group. The LV ejection fraction was more reduced in the chronic IMR group compared with the acute IMR group (37.1±11.1% versus 47.4±11.7%; *P*=0.025). There were no significant differences in the MR degree or pulmonary artery systolic pressure between the 2 groups.

MV apparatus parameters measured by 2D and 3D echocardiography are summarized in Table 2. The tenting parameters such as tenting height, tenting area, max tenting height, and tenting volume were significantly smaller in the acute IMR group than those in the chronic IMR group (*P*<0.001, *P*<0.001, *P*=0.017, *P*=0.008, respectively). Annular diameter and annular area were significantly smaller in the acute IMR group than in the chronic IMR group (*P*=0.001, *P*=0.008). Although there were no significant differences in posteromedial and anterolateral tethering lengths between the 2 groups, PM separation (distance between anterior and posterior PM tips) was significantly smaller in the acute IMR group than in the chronic IMR group

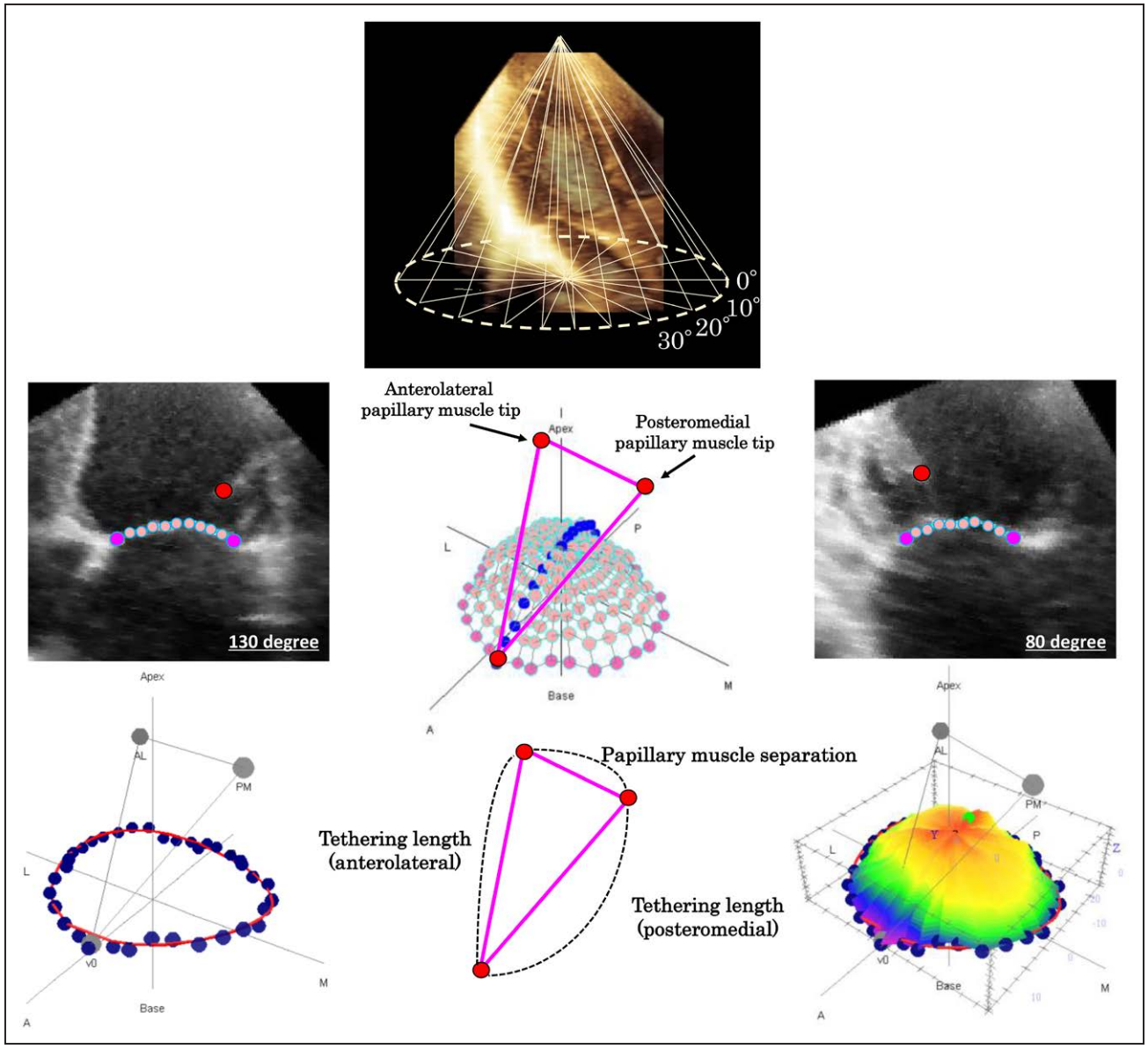


**Figure 1. Three-dimensional (3D) quantitative analysis of the mitral valve apparatus.**
The 3D data were automatically cropped into 18 radial planes spaced 10° apart. We manually marked the mitral annulus and leaflets in each cropped plane. Tips of the anterolateral papillary muscle and posteromedial papillary muscle were obtained and marked. From these data, anatomic 3D images of the mitral leaflets and annulus were reconstructed with the position of 2 papillary tips. Measurements of the interpapillary distance (papillary muscle separation), and tethering lengths between the anterior mitral annulus and AL papillary muscle and the PM papillary muscle are schematically shown. AL indicates anterolateral; and PM, posteromedial.

(*P*=0.030). The 3D-derived MV leaflet surface area was significantly smaller in the acute IMR group than in the chronic IMR group (5.78 [5.16–6.32] versus 7.56 [6.89–11.32] $cm^2/m^2$; *P*<0.001). The MV leaflet surface area/annular area ratio (leaflet area/annular area) was significantly smaller in the acute IMR group than in the chronic IMR group (1.08 [1.01–1.14] versus 1.28 [1.24–1.37]; *P*=0.001). Representative cases of acute IMR and chronic IMR are shown in Figure 2. The leaflet length was significantly shorter in the acute IMR group compared with the chronic IMR group, in both anterior and posterior leaflet (12.44±1.99 versus 14.28±2.35 $mm/m^2$, 7.56±1.15 versus 9.82±1.95 $mm/m^2$; *P*=0.013, *P*<0.001, respectively).

## Comparison With No-MR Groups and Non-MI Normal Controls

Three-dimensional–derived leaflet area in the acute IMR group was comparable with that in the AMI without MR group and non-MI normal group (5.78 [5.16–6.32] versus 5.98 [5.24–6.41] $cm^2/m^2$, 5.78 [5.16–6.32] versus 5.61 [4.76–6.41] $cm^2/m^2$; *P*=0.600, *P*=0.550, respectively). The leaflet/annular ratio was significantly

**Table 1. Patient Baseline Characteristics and Basic Echocardiographic Parameters**

| | Ischemic MR | | Control | | |
|---|---|---|---|---|---|
| | Acute IMR (n=44) | Chronic IMR (n=36) | AMI Without MR (n=20) | Previous MI Without MR (n=20) | Non-MI Normal (n=14) |
| Age, y | 75±10 | 74±11 | 74±10 | 71±9 | 72±7 |
| Male | 21 (47.7%) | 32 (88.9%) | 16 (80.0%) | 19 (95.0%) | 11 (78.6%) |
| Culprit vessel | | | | | |
| LAD | 20 (45.5%) | 22 (61.1%) | 9 (45.0%) | 15 (75.0%) | N/A |
| LCX | 4 (9.1%) | 2 (5.6%) | 2 (10.0%) | 1 (5.0%) | N/A |
| RCA | 16 (36.4%) | 12 (33.3%) | 8 (40.0%) | 4 (20.0%) | N/A |
| LMT | 4 (9.1%) | 0 (0.0%) | 1 (5.0%) | 0 (0.0%) | N/A |
| Multivessel disease | 25 (56.8%) | 25 (69.4%) | 10 (50.0%) | 13 (65.0%) | N/A |
| Heart rate, bpm | 78±18* | 77±16 | 77±18 | 71±13 | 70±14 |
| Systolic blood pressure, mm Hg | 148±29† | 124±33‡ | 142±23 | 128±16 | 125±21 |
| Diastolic blood pressure, mm Hg | 86±14*† | 66±12‡ | 76±12 | 70±13 | 70±14 |
| LV parameters | | | | | |
| LV end-diastolic diameter, mm/m$^2$ | 31.1 (28.4–33.7)*†‡§ | 35.3 (32.6–41.6)‡§ | 28.6 (26.4–30.1) | 35.0 (31.8–37.3) | 26.6 (25.5–28.2) |
| LV end-systolic diameter, mm/m$^2$ | 23.1 (20.5–24.9)*†‡§ | 29.4 (24.8–36.1)‡§ | 21.2 (18.6–21.8) | 26.8 (24.0–30.8) | 16.3 (14.6–18.2) |
| LV end-diastolic volume, mL/m$^2$ | 40.8 (33.1–48.3)*† | 88.8 (66.5–108.8)*‡§ | 40.4 (33.3–45.0) | 64.0 (49.6–83.1) | 36.7 (31.2–43.3) |
| LV end-systolic volume, mL/m$^2$ | 17.8 (17.0–30.1)*†§ | 49.5 (34.2–73.7)‡§ | 19.2 (13.1–23.3) | 34.0 (27.5–49.9) | 11.3 (9.0–14.0) |
| LV ejection fraction (%) | 47.4±11.7†§ | 37.1±11.1‡§ | 52.4±8.8 | 41.1±8.7 | 69.3±7.8 |
| MR degree | | | | | |
| Average vena contracta, mm | 6.1 (5.4–7.0)*‡ | 6.6 (5.4–8.1)*‡ | 2.6 (0.5–3.8) | 3.1 (2.9–3.9) | N/A |
| Regurgitant volume, mL | 46.6±9.9*‡ | 44.1±15.0*‡ | 10.1±9.3 | 16.9±6.8 | N/A |
| Pulmonary artery systolic pressure, mm Hg | 40.6 (28.7–50.3)*‡§ | 39.5 (30.0–57.9)*‡§ | 30.1 (23.8–37.2) | 29.0 (24.5–32.0) | 27.5 (25.0–33.5) |

Data are expressed as mean±SD, median (interquartile range), or n (%) of patients. AMI indicates acute myocardial infarction; IMR, ischemic mitral regurgitation; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; LMT, left main trunk; LV, left ventricular; MI, myocardial infarction; MR, mitral regurgitation; N/A, not applicable; and RCA, right coronary artery.

*$P$<0.05 vs previous MI without MR.

†$P$<0.05 vs chronic IMR.

‡$P$<0.05 vs AMI without MR.

§$P$<0.05 vs non-MI normal.

smaller in the acute IMR group compared with AMI without MR group (1.08 [1.01–1.14] versus 1.34 [1.27–1.41]; $P$<0.001). There were no significant differences in the tenting degree between the 2 groups in our population. Leaflet surface area in the chronic IMR group was significantly larger than normal controls (7.56 [6.89–11.32] versus 5.61 [4.76–6.41] cm$^2$/m$^2$; $P$<0.001). Leaflet area/annular area was significantly larger with higher coaptation length in the post-MI without MR group reflecting the smaller annular size compared with chronic IMR group (1.43 [1.37–1.50] versus 1.28 [1.24–1.37]; $P$<0.001).

The coaptation length both in the acute IMR group and in the chronic IMR group was significantly and similarly smaller than the non-IMR controls and in the non-MI normal group: acute IMR versus AMI without MR (1.54±0.21 versus 2.59±0.41; $P$<0.001), acute IMR versus non-MI normal (1.54±0.21 versus 2.52±0.43; $P$<0.001), chronic IMR versus previous MI without MR (1.36±0.49 versus 2.11±0.57; $P$<0.001), and chronic IMR versus non-MI normal (1.36±0.49 versus 2.52±0.43; $P$<0.001). Figure 3 shows (1) the relationship between the average vena contracta width and MV tenting area and (2) the relationship between the tenting area and LV systolic dimension in the acute IMR group and the chronic IMR group. The larger the MV tenting, the larger the MR progress in both acute and chronic IMR groups ($r$=0.559, $r$=0.800, respectively). Acute IMR progresses with smaller tenting compared with the chronic IMR. On one hand, tenting degree showed similar correlations with LV size between the 2 groups.

## Interobserver and Intraobserver Variability for 3D Measurements

A comparison of intraobserver showed good agreement between measurements, on mitral annular area ($r$=0.89) and tenting volume ($r$=0.82). The intraobserver variability was as follows: annular area, 4.6%, and tenting volume, 5.2%. Interobserver comparisons

**Table 2. Mitral Valve Apparatus Parameters Measured by 2D/3D Echocardiography**

| | Ischemic MR | | Control | | |
|---|---|---|---|---|---|
| | Acute IMR (n=44) | Chronic IMR (n=36) | AMI Without MR (n=20) | Previous MI Without MR (n=20) | Non-MI Normal (n=14) |
| 2D analysis | | | | | |
| Tenting area, $cm^2/m^2$ | 1.02 (0.82–1.15)*†‡ | 1.56 (1.28–1.77)†‡§ | 0.57 (0.53–0.68) | 0.85 (0.78–1.00) | 0.42 (0.37–0.44) |
| Tenting height, $mm/m^2$ | 5.25 (4.74–6.31)*†‡§ | 6.79 (6.27–7.62)†‡§ | 3.61 (3.31–4.13) | 4.79 (4.11–5.23) | 2.71 (2.46–2.86) |
| Annular diameter, $mm/m^2$ | 18.74 (17.44–20.50)*†‡ | 21.11 (19.05–22.66)†‡§ | 16.09 (15.61–16.84) | 17.99 (17.32–18.79) | 15.82 (14.51–16.60) |
| 3D analysis | | | | | |
| Max tenting height, $mm/m^2$ | 3.49 (2.27–4.85)*‡ | 5.13 (3.72–6.26)†‡ | 3.33 (2.50–3.89) | 3.94 (3.30–4.77) | 2.21 (1.76–3.20) |
| Tenting volume, $cm^3/m^2$ | 0.98 (0.66–1.68)*‡ | 1.88 (1.16–2.65)†‡§ | 0.77 (0.62–0.96) | 1.22 (0.77–1.75) | 0.53 (0.35–0.92) |
| Annular area, $cm^2/m^2$ | 5.17 (4.80–5.86)*† | 5.81 (5.47–8.22)†‡§ | 4.27 (4.03–4.99) | 4.67 (4.42–5.78) | 4.13 (3.94–5.04) |
| Tethering length, posteromedial; $mm/m^2$ | 20.58 (18.41–22.28) | 21.32 (19.73–25.31)‡ | 20.38 (18.24–23.79) | 22.37 (21.08–25.09) | 19.77 (18.27–20.69) |
| Tethering length, anterolateral; $mm/m^2$ | 19.81 (19.13–24.09)‡ | 20.62 (19.05–25.72)‡ | 19.70 (17.79–21.89) | 19.88 (18.09–22.93) | 17.55 (16.25–18.49) |
| Papillary muscle separation, $mm/m^2$ | 11.97±3.91* | 15.17±3.42†‡§ | 10.02±2.66 | 12.43±2.65 | 10.92±1.31 |
| Leaflet surface area, $cm^2/m^2$ | 5.78 (5.16–6.32)*§ | 7.56 (6.89–11.32)†‡§ | 5.98 (5.24–6.41) | 6.83 (6.09–8.17) | 5.61 (4.76–6.41) |
| Leaflet surface/annular area ratio | 1.08 (1.01–1.14)*†‡§ | 1.28 (1.24–1.37)§ | 1.34 (1.27–1.41) | 1.43 (1.37–1.50) | 1.26 (1.18–1.32) |
| Anterior leaflet length, $mm/m^2$ | 12.44±1.99*‡ | 14.28±2.35†‡§ | 12.53±1.74 | 12.87±1.97 | 11.07±1.49 |
| Posterior leaflet length, $mm/m^2$ | 7.56±1.15*†§ | 9.82±1.95†‡ | 8.83±1.39 | 9.02±1.67 | 6.95±1.35 |
| Coaptation length, $mm/m^2$ | 1.54±0.21*†‡§ | 1.36±0.49†‡§ | 2.59±0.41 | 2.11±0.57 | 2.52±0.43 |

Data are expressed as mean±SD or median (interquartile range). AMI indicates acute myocardial infarction; D, dimensional; IMR, ischemic mitral regurgitation; MI, myocardial infarction; and MR, mitral regurgitation.

*$P$<0.05 vs chronic IMR.

†$P$<0.05 vs AMI without MR.

‡$P$<0.05 vs non-MI normal.

§$P$<0.05 vs previous MI without MR.

showed good agreement for mitral annular area ($r$=0.79) and tenting volume ($r$=0.74). The interobserver variability were annular area, 6.7%, and tenting volume, 7.8%.

## DISCUSSION

In this study, we investigated the characteristics of MV complex geometry, including LV parameters and hemodynamic states, in acute IMR complicated with first-onset AMI, and compared the results with IMR caused by dilation or ischemic distortion of the LV myocardium underlying the PMs in the chronic phase after MI using transthoracic 3D echocardiography.

Previous experimental and clinical studies have proposed the MV tethering phenomenon as a major mechanism of IMR as a result of chronic LV remodeling after MI.[3–6,9,11] Two-dimensional and 3D echocardiography have greatly contributed to assess the complex mechanisms of MV remodeling and have quantitatively proven that the displacement of attached PMs tethers the mitral leaflets into the LV and restricts their coaptation.[3–6,9,11] However, these geometric mechanisms of IMR have been mostly based on IMR in the subacute or chronic period of MI,[3–6,9,11] and little has been evaluated on acute remodeling in the mitral complex as a result of sudden-onset LV dysfunction in the very first stage of AMI. We have recently reported the dynamic course of IMR from the emergency room to early and late post-PCI and have found that the degree of acute IMR can change positively and negatively after successful primary PCI.[2] The average tenting area measured in the 2D parasternal long-axis view in patients with acute IMR was relatively smaller compared with previously published studies on chronic IMR. Our previous results from the 2D analysis of MV imply the possibility of different mechanisms of IMR developing from acute onset MI. This is the first clinical study to investigate 3D MV complex geometry in patients with acute IMR complicated with first-onset AMI on their arrival at the emergency room.

### LV Remodeling in Acute IMR and Chronic IMR

LV systolic and diastolic volumes are significantly smaller in acute IMR than in chronic IMR despite a comparable degree of regurgitation. In these 2 groups, patients with chronic IMR had a much larger LV than AMI patients with acute IMR.

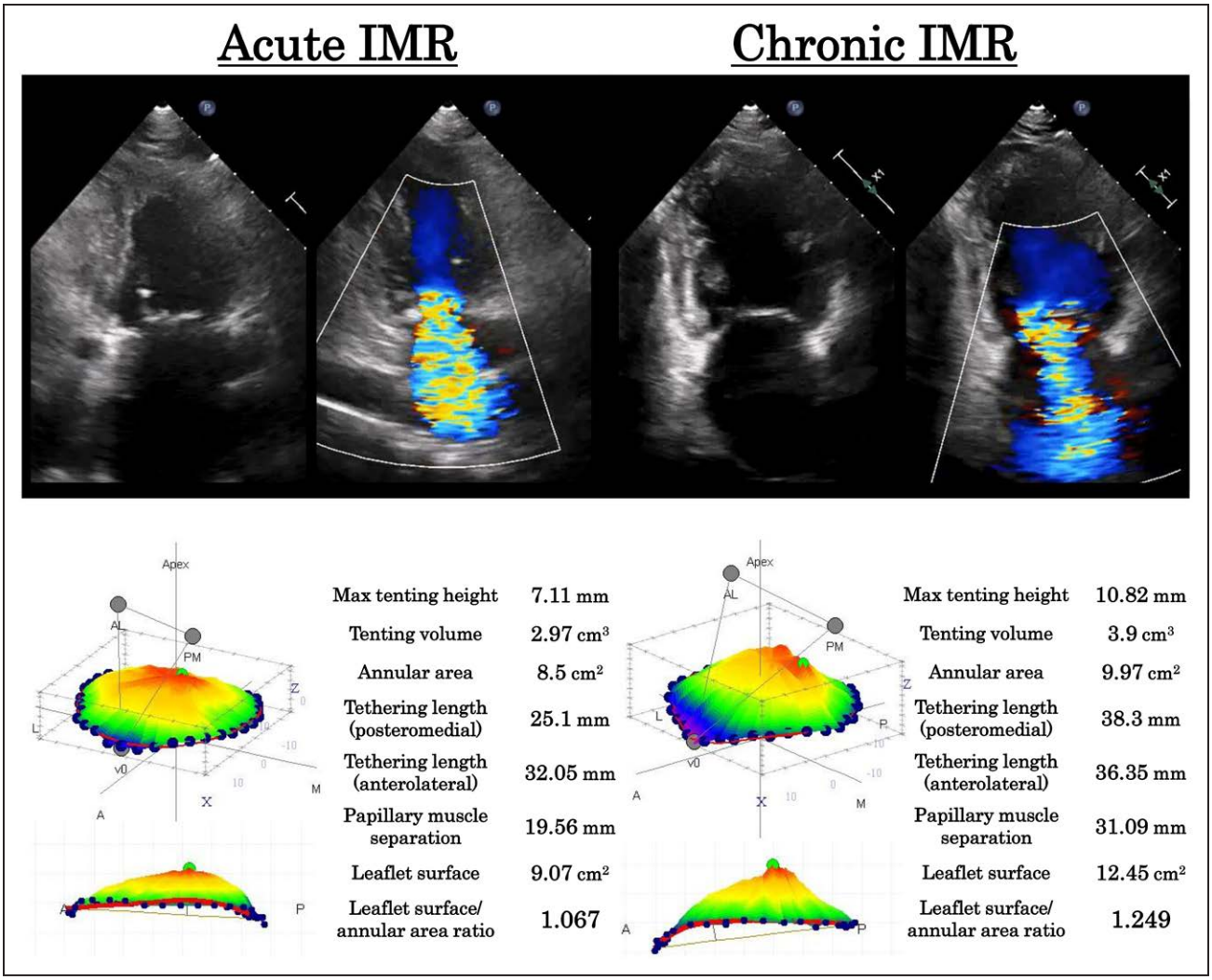


**Figure 2. Representative cases of acute and chronic ischemic mitral regurgitation (IMR).**
The regurgitant volumes of mitral regurgitation were almost the same and were classified as severe mitral regurgitation in 2 cases. While an acute IMR case (**left**) had a smaller tenting volume and annular area, a chronic IMR case (**right**) had a larger tenting volume and annular area. The leaflet surface is also clearly much smaller in acute IMR cases than in chronic IMR cases. These cases show that IMR can be observed even with a relatively mild degree of valve tethering in acute IMR cases compared with those in chronic IMR cases.

## MV Remodeling in Acute IMR and Chronic IMR

### *MV Tethering Parameters*

In our study population, the degree of mitral apparatus remodeling was modest in patients with first-onset AMI who developed significant IMR on arrival compared with the chronic IMR group. Smaller tenting volume and tenting height likely reflect the milder LV remodeling with a lower tethering force in acute IMR than chronic IMR. Of note, although there were no significant differences in the tethering lengths measured from the anterior annulus to both anterolateral and posteromedial PM tips, distances between both PMs were larger in chronic IMR than in acute IMR. These results suggest that IMR can be developed in smaller MV tenting in the acute phase of first-onset AMI compared with chronic IMR. Although both the tenting volume and height were smaller in the acute IMR patients, the annulus was also smaller compared with the chronic IMR group. As the tenting volume is influenced by the annular size, the tenting height is not as different between the 2 groups. Coaptation length was smaller in the chronic IMR group than in the acute IMR group.

### *Possible Role of Insufficient MV Leaflet Adaptation in the Progression of Acute IMR*

MV leaflet surface area measured by reconstructed 3D echocardiography was significantly larger in chronic stage post-MI patients with significant IMR compared with patients with AMI complicated with acute IMR. The chronic valve stretch phenomenon (valve adaptation) was firstly proposed by Chaput et al,[12] and they dem-

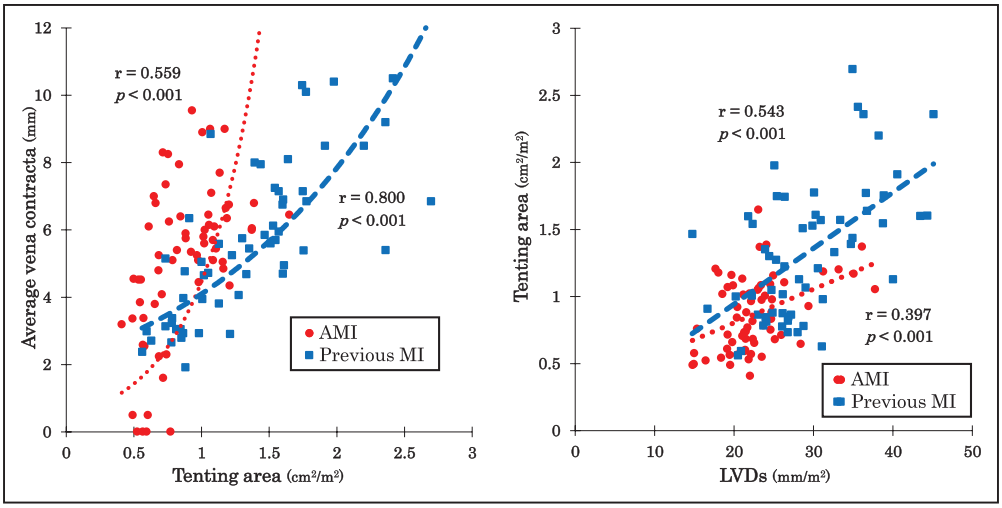


**Figure 3.** Degree of MR, valve tenting and LV size. The relationship between the average vena contracta width and MV tenting area (**left**). The larger the MV tenting, the larger the MR progresses in both AMI and previous MI groups. Acute IMR progresses with smaller tenting compared with the chronic IMR. The relationship between the tenting area and LVDs (**right**). Tenting degree showed similar correlations with LV size between the AMI group and previous MI group. AMI indicates acute myocardial infarction; IMR, ischemic mitral regurgitation; LVDs, left ventricular systolic dimensions; and MV, mitral valve.



onstrated that chronic mechanical stretches imposed by PM tethering increased the MV leaflet area which may compensate for ventricular remodeling to reduce the severity of functional MR. Subsequent studies have suggested some biological mechanisms of MV adaptation. Dal-Bianco et al[13,14] have published a series of in vivo experimental studies with regard to the active adaptation of the tethered MV, and they showed reactivated embryonic developmental pathways as a mechanism for the chronic histological change in the MV leaflet. They also proposed the contribution of $CD45^+$ and $CD31^+$ endothelial cells to MV adaptation and fibrosis after MI. This topic has yet to be well investigated in the clinical setting, and the present study is the first report that quantitatively measured the actual mitral leaflet surface area of the acutely infarct heart before the mitral adaptation process begins (or has just started). Our findings suggest that IMR can progress with modest valve tenting in the very acute phase of AMI, and leaflets without adaptation may yield to the tethering force from an acutely infarcted LV with relatively mild remodeling compared with chronic IMR caused by significant LV dilation and remodeling after infarction. Nevertheless, MV tenting degree in the acute IMR patients was still larger compared with the non-MI controls, which suggests that the valve tethering phenomenon because of acute LV dysfunction plays a major role in the acute IMR progression as the basic mechanism. It should also be notable that both acute and chronic IMR groups showed similarly reduced coaptation length compared with non-IMR controls and the non-MI normal group. This result suggests that the reduction in the valve coaptation is ultimately the final common pathway to cause IMR.

## Comparison Between MR Degree and MV Tenting Degree

Figure 3 shows that the acute IMR progresses in the smaller tenting compared with the chronic IMR, which support the conclusion of the present study. Interestingly, correlation between the MR degree and the tenting degree in the AMI patients was not as significant as the previous MI group. This may be because the multiple confounders including hemodynamics and valve function can easily affect the progression of acute IMR. On one hand, comparison between the tenting degree and the LV size showed only modest correlations in both AMI and previous MI groups with apparent overlaps, which possibly suggest the absence of chordae remodeling (elongation) in the chronic stage post-MI patients. Further investigation should be needed to clarify the role of MV and subvalvular remodeling in the progression of IMR.

## Comparison With No-MR Controls and Non-MI Controls

Leaflet area in the acute IMR group was comparable with that in the AMI without MR group and normal control group, which suggested the lack of valve adaptation in the acute phase of AMI. Of note, mitral annulus tended to flatten and dilated in the acute IMR group than that in the AMI without MR group resulted in the smaller leaflet to annular ratio and shorter coaptation length in the acute IMR group compared with AMI without MR group. There were no significant differences in the tenting degree between the 2 groups in our population. Higher estimated pulmonary artery

pressure in the acute IMR group would suggest the effect of higher left atrial pressure on the annular dilation and flattening, contributing the poor valve coaptation. These results provide convincing evidence that acute IMR might progress not simply by the tethering effect but also by the hemodynamic effect under the acute ischemic environment in patients with smaller leaflet, which is unprepared to the acute geometric and hemodynamic changes caused by AMI. Multiple confounding factors rather than just the degree of tethering should be taken into account in considering the mechanisms of acute IMR, and our results suggest that smaller leaflets with relatively large annulus would make them more vulnerable to pathological tethering despite the absence of significant LV remodeling. Possible contribution of the individual leaflet pathology to the occurrence of IMR at the onset of MI should be the next issue to be investigated. In addition, role of acute valve stretch should also be considered. Leaflet area in the acute IMR group and acute MI without MR group is comparable, with a mild increase in area than non-MI normal group. Although the increase in area in the AMI group was mild and not statistically significant, anterior leaflet length was significantly longer in the AMI groups than in the non-MI normal group.

## Hemodynamic Factors Contribute to the Development of Acute IMR

The present study provides new insights into the mechanism of acutely progressed IMR early after the onset of AMI. It has been well established that the degree of secondary MR changes along with the patient's hemodynamic condition. The impact of blood pressure on the severity of MR should be considered in the interpretation of the present study results. Average systolic and diastolic blood pressure were significantly higher in acute IMR patients than in chronic IMR patients. Higher blood pressure in the early stage of acute MI is a potential confounder of IMR development in AMI patients. There are elements other than pathological PM geometry due to ventricular remodeling that contribute to the imbalance between tethering and closing forces, i.e., LV systolic pressure, contractility and annular remodeling. Possible effects of the hemodynamics during AMI on the progression of acute IMR should be considered when we interpret our results. As we have already described, blood pressure was higher in the acute IMR than in the chronic IMR. Higher blood pressure can be a hemodynamic burden for the LV, but at the same time, higher blood pressure should also act as the higher closing force for the valve coaptation. Although the left atrial pressure is not known in this study, the comparable pulmonary artery pressure between the 2 groups suggests a higher closing force in the acute IMR group than in the chronic IMR. The similar MR progression despite higher closing force in the acute IMR group would make the conclusion of this study even stronger. The AMI without MR group also had higher blood pressure as well as the acute IMR group, but had lower pulmonary artery pressure compared with the acute IMR group. It is uncertain whether the pulmonary hypertension in the acute IMR group is a cause or result of significant IMR, but these results imply that the role of acute hemodynamic burden plays an important role in the progression of acute IMR.

## Clinical Implications

IMR has been recognized as a clinically important complication after MI that can worsen the long-term prognosis. The role of surgical repair is still controversial with limited and conflicting data based on various surgical strategies for heterogeneous patterns of LV remodeling depending on each patient's infarct region. Moreover, recent advances in catheter intervention for MR are expected as an alternative therapy for secondary MR. IMR is highly dynamic, especially during the acute phase of ischemia over the course of emergency revascularization. We have recently reported the dynamic course of IMR from the emergency room to the chronic phase after primary PCI, and the presence of acute IMR in patients with first-onset AMI had an adverse 30-day prognosis after successful primary PCI. Clarifying the mechanisms of IMR development from the early stage to the chronic stage after MI is needed for the development of appropriate therapeutic strategies for the complex pathology. The results of the present study should be the first step in understanding the pathology of acute IMR in the clinical setting. Serial changes in the MV complex geometry over the course of MI should be investigated to reach a further understanding of the complex mechanisms of IMR.

## Limitations

First, the present study had a relatively limited study population, which was restricted to patients who fulfilled predefined inclusion criteria. Further investigations are needed to clarify the geometric heterogeneities in various types of patients. Second, the method for measuring leaflet area in the present study minimizes but cannot completely avoid the effect of coapted area at the onset of valve closure. This limitation might result in underestimation of the total valve leaflet area. However, leaflet lengths measured in diastole on the 3D-oriented middle portion of the anterior leaflet and posterior middle scallop showed shorter leaflet length in the acute IMR group than in the chronic IMR group, which support the results of 3D analysis. Third, the preexistence of MR before MI cannot be excluded. This

limitation is shared by most studies in this area. We excluded patients with primary (organic) MR wherever possible. Finally, in this study, the relationship between the MV remodeling pattern and infarct region of the myocardium or culprit coronary lesion was not evaluated. Further investigation in a larger population using 2D/3D echocardiography is necessary to analyze the possible heterogeneity in the mitral apparatus geometry based on the infarct region.

## Conclusions

Sudden-onset LV dysfunction in AMI may cause loss of MV coaptation even with a relatively mild degree of valve tethering. Compared with previously studied chronic IMR, a smaller leaflet area without leaflet adaptation and a larger hemodynamic burden at the acute onset of MI would result in clinically significant IMR despite relatively small leaflet tethering.

## ARTICLE INFORMATION

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### Disclosures

None.

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# Acute Versus Chronic Ischemic Mitral Regurgitation: An Echocardiographic Study of Anatomy and Physiology

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