Different Mechanisms of Ischemic Mitral Regurgitation in Patients With Inferior and Anterior Myocardial Infarction

Hui Zhang, MD*, Yutaka Otsuji, MD***, Takeshi Uemura, MD*, Bo Yu, MD*, Masaaki Takeuchi, MD***, Shuichi Hamasaki, MD*, Masaaki Miyata, MD*, Akira Kisanuki, MD*, Shinichi Minagoe, MD*, Robert A. Levine, MD** and Chuwa Tei, MD*

*Department of Cardiovascular, Respiratory and Metabolic Medicine, Graduate School of Medicine, Kagoshima University, Kagoshima, Japan

**Cardiac Ultrasound Laboratory, Massachusetts General Hospital, Boston, MA, USA

***Second Department of Internal Medicine, University of Occupational and Environmental Health, School of Medicine, Kitakyushu, Japan

Abstract

Background. Basic mechanism of ischemic mitral regurgitation (MR) is displacement of papillary muscles (PMs) due to left ventricular (LV) remodeling. Variability in LV remodeling can potentially cause heterogeneous PM displacements. The aim of this study is to compare the mitral valve complex geometry in patients with ischemic MR due to inferior and anterior myocardial infarction (MI).

Methods. In 33 patients with prior inferior MI, 61 with anterior MI, and 22 controls, LV volume, mitral annular area, PM tethering distance, and MR were quantified by echocardiography.

Results. Significant MR (MR fraction > 20%) was observed in 12 of the 33 with inferior MI and 7 of the 61 with anterior MI. In patients with MR due to inferior MI, tethering distance was significantly longer in medial compared to lateral PM (42.6 ± 4.9 vs. 36.1 ± 1.7 mm, $p < 0.001$), demonstrating asymmetric medial PM displacement. Patients with MR due to anterior MI had comparable increases in both PM tethering distances (41.0 ± 2.4 vs. 41.4 ± 1.8 mm, n.s.), demonstrating symmetric bilateral PM displacement.

Conclusions. Although patients with ischemic MR due to inferior MI have asymmetrically predominant medial PM displacement, those with ischemic MR due to anterior MI have symmetric bilateral PM displacements.

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Key words: echocardiography, mitral regurgitation, left ventricular remodeling, ischemic heart disease

Introduction

Ischemic mitral regurgitation (MR) presents a challenging clinical problem associated with suboptimal surgical outcome and poor prognosis [1-7]. Augmented leaflet tethering by the outward displacement of papillary muscles (PMs) due to left ventricular

(LV) remodeling is the basic mechanism of ischemic MR with apically displaced leaflets (Figure 1) [8-18]. Ischemic MR frequently develops in patients with inferior myocardial infarction (MI) and also in those with anterior MI [19-21]. Differences in the characteristics of LV remodeling in inferior and anterior MI suggests different mechanisms of ischemic MR in these patients. However, the differences in the mechanism are not fully investigated.

LV remodeling after inferior MI results in predominant displacement of the medial PM with only modest displacement of lateral PM or asymmetric medial PM displacement, which contributes to the development of ischemic MR (Figure 2, left panel) [12, 19]. In contrast, patients with anterior MI develop LV remodeling, which occurs predominantly in the anteroseptal and

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Address for correspondence: Yutaka Otsuji, MD
Second Department of Internal Medicine, University of Occupational and Environmental Health, School of Medicine,
1-1 Iseigaoka, Yahatanishi-ku, Kitakyushu, 807-8555, Japan.
Telephone: +81-93-691-7250
Fax: +81-93-691-6913
E-mail: otsujiy@med.uoeh-u.ac.jp
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Fig. 1. A scheme illustrating the basic mechanism of ischemic mitral regurgitation (MR). Left ventricular (LV) remodeling causes outward displacement of papillary muscles (PM), which augments leaflet tethering and induce apical displacement of mitral leaflets and MR.

Fig. 2. Potentially different mechanisms of ischemic MR due to inferior and anterior myocardial infarction (MI). LV remodeling after inferior MI leads to predominant displacement of the medial PM with only modest displacement of lateral PM, resulting in asymmetric displacement of PMs with ischemic MR. In contrast, anterior MI can potentially causes significant remodeling in antero-septal and apical LV wall, resulting in symmetric displacement of both PMs to cause ischemic MR.

apical region and can potentially cause displacement of both PMs or symmetric PM displacement, resulting in a different mechanism of ischemic MR from that in inferior MI (Figure 2, right panel). Therefore, the purpose of this study is to compare the geometry of mitral valve complex in patients with significant ischemic MR

due to inferior and anterior MI to test the hypothesis.

Methods

Study population

Subjects consisted of 22 normal control subjects, 33 consecutive patients with prior inferior MI, and 61 con-

secutive patients with prior anteroapical MI. Inclusion criteria was the presence of prior inferior or anteroapical MI diagnosed on the basis of 1) a history of acute MI more than 1 month before with increased serum creatine kinase levels above twice the upper normal value and 2) segmental LV wall motion abnormality of the inferior or anteroapical wall. Exclusion criteria were recent MI (< 1 month), multiple MIs, previous heart surgery, MR caused by organic mitral valvular lesions (including rheumatic changes, chordal or PM rupture, and infective endocarditis), and other associated cardiac diseases, such as aortic valve or congenital heart disease. Normal control subjects had normal echocardiograms without known cardiovascular disease. Written informed consent was obtained from all subjects and institutional committee of Kagoshima University approved the study protocol.

Echocardiographic measurements

All patients were referred for echocardiographic assessment between November 2002 and April 2003. Standard 2-dimensional and Doppler echocardiography examinations with color flow mapping were performed with the patients in the left lateral decubitus position using commercially available diagnostic systems (ATL HDI 3000, Bothell, Wash, USA; Toshiba SSH 380A, Tokyo, Japan; and Philips Medical Systems, Sonos 5500, Andover, Mass, USA). Special attention was paid to visualization of the lateral and medial PM tips in apical 4- and 2-chamber views. LV end-diastolic and end-systolic cavity areas were traced in those views, and LV volumes and ejection fractions (EFs) were obtained by using the modified biplane Simpson's method [22]. The LV wall was divided into 16 segments, and the number of segments with wall motion abnormality was estimated to evaluate the spatial extent of ischemic LV dysfunction. Midsystolic mitral annular dimension was measured in the apical 4- and 2-chamber views, and its area was calculated with an ellipsoid assumption (annular area = $d_1 \times d_2 \times \pi / 4$) [23, 24]. The mitral annulus was identified as the leaflet hinge point. End-diastolic, end-systolic, and mid-systolic frames were determined as the initial, last, and middle frames with systolic mitral leaflet closure. The mitral leaflet tenting area between the leaflets and the line connecting the annular hinge points in the apical 4-chamber view was traced at mid-systole to estimate the apical displacement of the mitral leaflets [8-10]. The leaflet tethering distance between the PM tips and the contralateral anterior mitral annulus was

also measured in the apical 4- and 2-chamber views by using the anterior mitral annulus as a reference point to estimate PM displacement (Figure 3) [10, 12, 19]. MR volume was calculated as the difference between mitral filling volume and aortic forward stroke volume obtained by the product of mitral or aortic annular area and the flow velocity time integral at the level using pulsed Doppler echocardiography [25]. Mitral filling volume was quantified as the difference between LV end-diastolic and end-systolic volumes in patients with suboptimal Doppler recordings and without aortic regurgitation [10]. MR fraction was then calculated as MR volume divided by mitral filling volume; MR fraction $\geq 20\%$ was considered as significant [14].

Reproducibility of measurements

Two independent observers repeated measurements of PM tethering distance from 10 patients' echocardiographic recordings. The differences in their measurements were used to express interobserver variability. The same observer repeated the measurements to estimate intraobserver variability.

Statistical analysis

Results were expressed as means $\pm$ SD. Variables were compared between groups by using the paired

Fig. 3. Methods to measure 1) the mitral annular area from 2 diameters in apical views, 2) the mitral leaflet-tenting area between the mitral leaflet and a line connecting mitral annular hinge points in the mid-systolic apical 4-chamber view (dashed area shown in the left panel), and 3) papillary muscle (PM) leaflet-tethering lengths between lateral or medial PM tips and contralateral anterior mitral annulus (ℓ_1 and ℓ_2). LV: Left ventricle, LA: left atrium, RV: right ventricle, RA: right atrium.

and/or unpaired Student *t* test. Incidences in 2 groups were compared by using the χ^2 test. Determinants of the mitral leaflet tenting area and severity of MR in patients with inferior and anterior MI were explored by entering the end-diastolic and end-systolic LV volumes, EF, mitral annular area, and PM-leaflet tethering distance into stepwise multiple regression analysis. A value of $p < 0.05$ was considered statistically significant.

Results

Comparisons between entire patients with inferior and anterior MI (Table 1)

Compared to patients with inferior MI, patients with anterior MI had significantly greater LV dilatation and reduction in EF. Mitral annular area and lateral PM tethering length were significantly increased for both groups compared to controls but without significant

difference between the 2 groups. In contrast, medial PM tethering length was significantly lengthened for both groups, and the elongation was significantly less in anterior compared to inferior MI. Consequently, the sum of tethering distances of both PMs was significantly greater in both groups than that of control group, but was again significantly less in patients with anterior MI. Increase in mitral leaflet tenting area as well as MR fraction were also significant in both groups, and these increases were again significantly less in anterior compared to inferior MI, which resulted in significantly lower incidence of significant MR in anterior compared to inferior MI. These 12 patients with significant ischemic MR due to inferior MI and 7 with MR due to anterior MI were enrolled to study subgroups for further comparison.

Table 1. Clinical and echocardiographic characteristics.

	Control (n=22)	Inferior MI (n=33)	vs.	Anterior MI (n=61)	<i>p</i> Value
Age (y)	65 ± 12	66 ± 9		66 ± 11	n.s.
Gender (M/F)	18 / 4	28 / 5		54 / 7	n.s.
Heart failure	0 / 22	4 / 33		6 / 61	n.s.
Time lapse after acute MI (mo)	0 ± 0	29 ± 35		27 ± 32	n.s.
LVEDV (ml)	91 ± 11	106 ± 19		125 ± 45	< 0.01
LVESV (ml)	38 ± 13	52 ± 30		71 ± 34	< 0.01
LVEF (%)	63 ± 6	49 ± 8		44 ± 7	< 0.01
Number of LV segments with asynergy	0 ± 0	1.8 ± 0.7		5.8 ± 2.2	< 0.001
Mitral Annular Area (cm ²)	7.8 ± 0.8	9.2 ± 1.3		8.9 ± 1.4	n.s.
PM Tethering Distance					
ℓ_1 (lateral PM) (mm)	33.5 ± 2.2	35.5 ± 1.9		35.1 ± 3.3	n.s.
ℓ_2 (medial PM) (mm)	33.4 ± 2.1	38.8 ± 4.9		34.9 ± 3.3	< 0.001
$\ell_1 + \ell_2$ (mm)	66.9 ± 3.7	74.1 ± 5.6		70.0 ± 6.4	< 0.001
Mitral Tenting Area (cm ²)	0.11 ± 0.08	0.76 ± 0.52		0.58 ± 0.35	< 0.05
MR fraction (%)	2 ± 5	17 ± 13		7 ± 9	< 0.001
Incidence of MR Fraction ≥20%	0 / 22 (0%)	12 / 33 (36%)		7 / 61 (11%)	< 0.01

MI: myocardial infarction, LVEDV: left ventricular end-diastolic volume, LVESV: left ventricular end-systolic volume, LVEF: left ventricular ejection fraction, ℓ_1 : lateral PM tethering distance, ℓ_2 : medial PM tethering distance, MR: mitral regurgitation.

Comparisons between patients with significant MR due to inferior and anterior MI (Table 2)

Comparisons between patients with significant MR due to inferior and anterior MI revealed that increase in LV end-diastolic and end-systolic volume and reduction in LVEF were significantly greater in ischemic MR due to anterior MI compared to inferior MI. Mitral annular dilatation was comparable. Elongation of lateral PM tethering distance was greater in ischemic MR due to anterior MI whereas the increase in medial and sum of PM tethering distances were comparable. These resulted in predominant or asymmetric increase in medial PM tethering distance in MR due to inferior MI and symmetric increase in both PM tethering dis-

tances in MR due to anterior MI (Figure 4). Although mitral leaflet tenting area was comparable between the 2 groups, MR fraction was significantly less in significant MR due to anterior MI compared to the MR due to inferior MI, suggesting that asymmetric PM displacement may cause greater MR when the sum of PM tethering was comparable.

Figure 5 shows two representative patients: one with ischemic MR due to inferior MI associated with asymmetric and predominant increase in medial PM tethering distance and another with ischemic MR due to anterior MI associated with symmetric increase in both PM tethering distances.

Table 2. Comparisons between patients with ischemic MR due to inferior and anterior MI.

	MR due to Inferior MI (n=12)	vs.	MR due to Anterior MI (n=7)	<i>p</i> Value
LVEDV (<i>ml</i>)	126 ± 11		197 ± 63	< 0.05
LVESV (<i>ml</i>)	76 ± 25		128 ± 43	< 0.001
LVEF (%)	46 ± 6		36 ± 4	< 0.01
Mitral Annular Area (<i>cm</i> ²)	10.5 ± 1.4		9.7 ± 1.1	n.s.
PM Tethering Distance				
ℓ_1 (<i>mm</i>)	36.1 ± 1.7		41.4 ± 1.8	< 0.05
ℓ_2 (<i>mm</i>)	42.6 ± 4.9		41.0 ± 2.4	n.s.
$\ell_1 + \ell_2$ (<i>mm</i>)	78.7 ± 6.0		82.4 ± 3.8	n.s.
Mitral Tenting Area (<i>cm</i> ²)	1.3 ± 0.4		1.2 ± 0.2	n.s.
MR fraction (%)	32 ± 9		27 ± 5	< 0.001

Abbreviations: as in Table 1.

Fig. 4. Bar graphs showing predominant and asymmetric increase in tethering distance of medial papillary muscle (PM) in ischemic MR with inferior MI (left panel) and symmetric increases in tethering distance of both PMs in ischemic MR with anterior MI (right panel).

Fig. 5. The patient with ischemic MR due to inferior MI (upper panels) showed an asymmetric displacement of PMs with predominantly longer tethering distance of medial (upper-right panel) compared to lateral PM. In contrast, symmetric displacement of both PMs was demonstrated in another patient with ischemic MR due to anterior MI with comparably elongated tethering distance of both PMs (lower panels).

Determinants of mitral leaflet tenting area and MR fraction

Multiple geometric indices showed significant relations with mitral leaflet tenting area in both patients with inferior as well as anterior MI by univariate analysis (Table 3). Multivariate analysis identified increase in medial PM tethering distance along with increase in LVEDV as the independent determinants of the leaflet tenting area in patients with inferior MI. In contrast, the increase in the sum of PM tethering distances was selected as the only independent determinant of the tenting area in patients with anterior MI. These suggest that asymmetric medial PM displacement is the major determinant of mitral leaflet tenting area in

patients with inferior MI, while symmetric displacement of both PMs is the determinant in anterior MI.

Similarly, multiple geometric indices showed significant relations with MR fraction in both patients with inferior as well as anterior MI by univariate analysis (Table 4). Multivariate analysis identified increase in medial PM tethering distance along with increase in LVEDV as the independent determinant of MR fraction in patients with inferior MI, while the sum of both PM tethering distances along with increase in LVESV were selected as independent determinants in patients with anterior MI. These results again suggest that asymmetric medial PM displacement is the major determinant of MR fraction in patients with inferior MI, while

Table 3. Determinants of mitral leaflet tenting area.

Univariate Analysis	Inferior MI (n = 33)		Anterior MI (n = 61)	
	r^2	p value	r^2	p value
LV EDV	0.48	< 0.0001	0.39	< 0.0001
LV ESV	0.25	< 0.005	0.38	< 0.0001
LV EF	0.04	n.s.	0.17	< 0.001
LAD	0.11	n.s.	0.06	n.s.
Mitral Annular Area	0.25	< 0.005	0.07	< 0.05
l_1	0.12	< 0.05	0.58	< 0.0001
l_2	0.65	< 0.0001	0.66	< 0.0001
$l_1 + l_2$	0.59	< 0.0001	0.67	< 0.0001
Multivariate Analysis	Coefficient		Coefficient	
		p value		p value
LV EDV	0.01	< 0.0001	(-)	n.s.
LV ESV	(-)	n.s.	(-)	n.s.
LV EF	(-)	n.s.	(-)	n.s.
LAD	(-)	n.s.	(-)	n.s.
Mitral Annular Area	(-)	n.s.	(-)	n.s.
l_1	(-)	n.s.	(-)	n.s.
l_2	0.07	< 0.0001	(-)	n.s.
$l_1 + l_2$	(-)	n.s.	0.04	< 0.0001

Abbreviations: as in Table 1.

Table 4. Determinants of MR fraction.

Univariate Analysis	Inferior MI (n = 33)		Anterior MI (n = 61)	
	r^2	p value	r^2	p value
LV EDV	0.59	< 0.0001	0.38	< 0.0001
LV ESV	0.39	< 0.0001	0.42	< 0.0001
LV EF	0.11	n.s.	0.25	< 0.001
LAD	0.24	< 0.005	0.09	< 0.05
Mitral Annular Area	0.39	< 0.0005	0.44	< 0.0004
l_1	0.13	< 0.05	0.65	< 0.0001
l_2	0.64	< 0.0001	0.62	< 0.0001
$l_1 + l_2$	0.59	< 0.0001	0.67	< 0.0001
Multivariate Analysis	Coefficient		Coefficient	
		p value		p value
LV EDV	0.33	< 0.0001	(-)	n.s.
LV ESV	(-)	n.s.	0.001	< 0.0001
LV EF	(-)	n.s.	(-)	n.s.
LAD	(-)	n.s.	(-)	n.s.
Mitral Annular Area	(-)	n.s.	(-)	n.s.
l_1	(-)	n.s.	(-)	n.s.
l_2	1.60	< 0.0001	(-)	n.s.
$l_1 + l_2$	(-)	n.s.	0.011	< 0.0001

Abbreviations: as in Table 1.

PM displacement is the determinant in those with anterior MI.

Reproducibility of measurements

Inter- and intra-observer variabilities for the measurements of PM leaflet-tethering distance were 1.5 ± 0.8 and 0.9 ± 0.5 mm or $4.1 \pm 2.2\%$ and $2.3 \pm 1.5\%$ of

the mean value, respectively.

Discussion

Different mechanisms of ischemic MR due to inferior and anterior MI

The basic mechanism of ischemic MR is leaflet teth-

ering due to outward displacement of PMs with LV remodeling (Figure 1) [8-21]. Both inferior as well as anterior MI cause ischemic MR [19-21]. Because the characteristics of LV remodeling are different between patients with inferior and anterior MI, it is expected that ischemic MR due to inferior and anterior MI may have different mechanisms. Asymmetric and predominant displacement of medial PM has been shown to cause ischemic MR in inferior MI (Figure 2) [12, 19-21]. However, the mechanism of ischemic MR due to anterior MI has not been fully investigated. Broad involvement of LV remodeling, including the apex and antero-septal wall, in anterior MI suggests that symmetric displacement of both PMs can be the mechanism of its ischemic MR (Figure 2). The present study demonstrated asymmetrically elongated medial PM tethering distance in patients with ischemic MR due to inferior MI and symmetrically elongated medial and lateral PM tethering distances in patients with the MR due to anterior MI. Therefore, the present study demonstrated that leaflet tethering is the basic mechanism of ischemic MR both in inferior and anterior MI. However, the nature of leaflet tethering is different between inferior and anterior MI: asymmetric and predominant displacement of medial PM in inferior MI and symmetric displacement of both PMs in anterior MI.

Relation to previous studies

Multiple investigations have shown that basic mechanisms of ischemic MR is leaflet tethering by PM displacement with LV remodeling [8-21]. The present study confirmed the importance of leaflet tethering in the development of ischemic MR and further demonstrated different characteristics of leaflet tethering or asymmetric and symmetric PM displacements in patients with ischemic MR due to inferior and anterior MI.

Importance of asymmetric and symmetric PM displacements have been demonstrated in *in vitro* studies [26]. Symmetric PM tethering causes the coaptation line to shift apically but parallel to the annular plane, while asymmetric PM tethering causes an uneven coaptation line with greater leaflet displacement at the side of asymmetrically displaced PM. Kwan et al. recently demonstrated asymmetric and symmetric deformation of mitral leaflets in patients with infero-posterior MI and those with dilated cardiomyopathy, suggesting that the nature of leaflet tethering can be different according to the disease entity [27]. The pre-

sent study confirmed these studies and further demonstrated heterogeneous deformity of mitral valve complex or asymmetric and symmetric PM displacements in ischemic MR due to inferior and anterior MI.

Clinical implications

Different mechanisms of ischemic MR, presented in this study, highlight the importance of different or tailored strategies and procedures of treatment for individual patients. Although current annuloplasty is effective to repair ischemic MR [28, 29], the results can be suboptimal [30]. Interventions, which help restore the balance of bilateral tethering forces imposed on mitral leaflets, can be more efficient in patients with ischemic MR. Results of the current study encourages further development of procedures targeted to restore medial PM malposition in patients with inferior MI and those targeted to restore malpositions of both PMs in anterior MI.

Limitations

In this study, different natures of geometric distortion of the mitral valve apparatus in ischemic MR due to inferior and anterior MI were demonstrated. Characteristics of outward displacements of medial and lateral PMs were different between inferior and anterior MI. This study demonstrated utility of echocardiography to evaluate mitral valve pathophysiology [31]. However, antero-posterior, medio-lateral, and baso-apical components of PM displacements were not investigated. Further 3-dimensional study is necessary to clarify these spatial components [32, 33]. Grade of ischemic MR was generally mild to moderate, and there was no patient with severe MR and regurgitant fraction > 50%. This is due to the fact that grade of ischemic MR is usually mild in most patients [2]. Therefore, mechanisms of severe ischemic MR due to inferior and anterior MI were not investigated. However, it is still important to investigate the mechanism of mild to moderate ischemic MR because mild degree of ischemic MR is also a significant risk that affects patient prognosis [2]. Although the current study demonstrated different mechanisms of ischemic MR due to inferior and anterior MI, corresponding procedures to repair the mitral valve were not demonstrated. Multiple novel approaches to repair ischemic MR are under aggressive investigations [34-38]. However, approaches to correct deformed mitral valve apparatus, causing ischemic MR, are not established. Further investigations are required to establish efficient meth-

ods to repair ischemic MR.

Nevertheless, understanding the pathophysiology is a prerequisite to successful repair of ischemic MR, and the purpose of this study was achieved by demonstrating different mechanisms of ischemic MR due to inferior and anterior MI, with potential applications for LV plasty targeted to heterogenous deformations of mitral valve apparatus in individual patients.

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