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Papillary Muscle Dysfunction Attenuates Ischemic Mitral Regurgitation in Patients With Localized Basal Inferior Left Ventricular Remodeling

Insights From Tissue Doppler Strain Imaging

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OBJECTIVES The purpose of this research was to test whether papillary muscle (PM) dysfunction attenuates ischemic mitral regurgitation (MR) in patients with left ventricular (LV) remodeling of a similar location and extent.

BACKGROUND Papillary muscle dysfunction could attenuate tethering and MR because of PM elongation. However, variability in the associated LV remodeling, which exaggerates tethering, can influence the relationship between PM dysfunction and MR.

METHODS In 40 patients with a previous inferior myocardial infarction but without other lesions, the LV volume, sphericity, PM tethering distance, PM longitudinal systolic strain, and MR fraction were quantified by echocardiography. The patients were divided into two groups: group 1 with significant basal inferoposterior LV bulging but without advanced LV bulging involving other territories, therefore with a similar location and extent of LV remodeling, and group 2 without significant LV bulging.

RESULTS The medial PM tethering distance was significantly correlated with the %MR fraction (r^2 = 0.64, $p < 0.01$), and multiple regression analysis identified an increase in the tethering distance as the only independent determinant of the MR fraction in all subjects and also in group 1. The PM longitudinal systolic strain had no significant relationships with MR fraction in all subjects with variable degrees of LV remodeling, but it had a significant inverse correlation with the MR fraction (r^2 = 0.33, $p < 0.01$) in group 1 with LV remodeling of a similar location and extent, indicating that PM dysfunction is associated with less MR.

CONCLUSIONS Papillary muscle dysfunction, reducing its longitudinal contraction to induce leaflet tethering, attenuates ischemic MR in patients with basal inferior LV remodeling. (J Am Coll Cardiol 2005;46:113–9) © 2005 by the American College of Cardiology Foundation

Ischemic mitral regurgitation (MR) is a common complication in patients with ischemic heart disease, and adversely affects their prognosis (1–3). Papillary muscle (PM) contractile dysfunction has previously been considered the main cause of ischemic MR with leaflet prolapse (4,5). However, isolated PM dysfunction failed to cause ischemic MR in animal models (6–9). In addition, mitral leaflet prolapse, which can be caused by PM dysfunction (4,5), is rare in patients with ischemic MR (10–12). Therefore, the relationship between PM dysfunction and ischemic MR has not been established.

Recent studies have demonstrated that the main cause of ischemic MR is augmented leaflet tethering by outward displacement of the PM due to left ventricular (LV) remodeling (Fig. 1, middle panel) (13–21). From the standpoint of leaflet tethering, remodeling of the adjacent LV wall to the PM in patients with ischemic heart disease can augment this tethering and MR (Fig.1, middle panel). However, in the presence of adjacent LV wall remodeling, PM dysfunction per se, with less systolic shortening in its long-axis direction, can potentially attenuate leaflet tethering and ischemic MR (Fig. 1, right panel). Therefore, ischemic MR basically relates to PM tethering, and PM dysfunction may not have a consistent relationship with MR in patients with variable degrees of adjacent LV wall remodeling. However, in selected patients with a similar degree of adjacent LV wall remodeling, PM dysfunction can potentially attenuate tethering and MR. Therefore, we hypothesized that ischemic MR basically relates to PM tethering but that PM dysfunction does not have a consistent relationship with the severity of MR in patients with variable degrees of LV remodeling. However, PM dysfunction may attenuate MR in patients with LV remodeling of a similar location and extent. The purpose of this study was to investigate the relationship between PM tethering, PM function, and ischemic MR in patients with prior inferior myocardial infarction (MI).

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Abbreviations and Acronyms

EDV = end-diastolic volume
EF = ejection fraction
LV = left ventricle/ventricular
MAA = mitral annular area
MI = myocardial infarction
MR = mitral regurgitation
PM = papillary muscle
2D = two-dimensional

METHODS

Study patients. The study included 40 consecutive patients with prior inferior MI who were referred for echocardiographic examination between October 2003 and January 2004. The inclusion criteria were the presence of prior inferior MI diagnosed on the basis of a history of acute MI more than one month previously, serum creatine kinase activities more than twice the upper normal value, and segmental LV wall motion abnormalities in the inferior wall. The exclusion criteria were recent MI (<1 month), multiple MIs, MR caused by intrinsic mitral valvular lesions (including rheumatic changes, infective vegetations, and chordal or PM rupture), and other cardiac diseases, such as congenital defects, cardiomyopathy, aortic valve or pericardial diseases. This study was performed with the patients' written informed consent.

Echocardiography. Standard two-dimensional (2D) and Doppler echocardiography with tissue Doppler strain imaging was performed using a 3- to 4.5-MHz transducer (Vivid 7, GE Medical Systems, Milwaukee, Wisconsin). Recordings of the apical four- and two-chamber views were done with special attention paid to visualize the PM; LV end-diastolic and end-systolic cavity areas were traced in those views, and the LV end-diastolic volume (EDV) and ejection fractions (EF) were calculated by the method of discs. The LV shape, or sphericity, was assessed using the LV short-to-long axis dimension ratio in the mid-systolic apical two-chamber view (Fig. 2) (22), and the mid-systolic mitral annular area (MAA) was obtained by determining the annular dimensions in the apical four- and two-chamber views based on assuming an elliptical geometry (MAA = $d_1 \times d_2 \times \pi/4$) (23). The leaflet-tethering distance between the PM tip and the contralateral anterior mitral annulus was also measured in the apical four- and two-chamber views in mid-systole (Fig. 2, ℓ_1 and ℓ_2) (24). The mitral filling volume was measured by Doppler echocardiography as the product of the diastolic MAA and the time-velocity-integral of the mitral filling flow at the annular level, and the aortic ejection stroke volume was measured as the product of the aortic annular area and the time-velocity-integral of the ejection flow. The MR volume was then calculated as the difference between the mitral filling volume and the aortic ejection volume, and the MR fraction was obtained as the MR volume divided by the mitral filling volume (25,26).

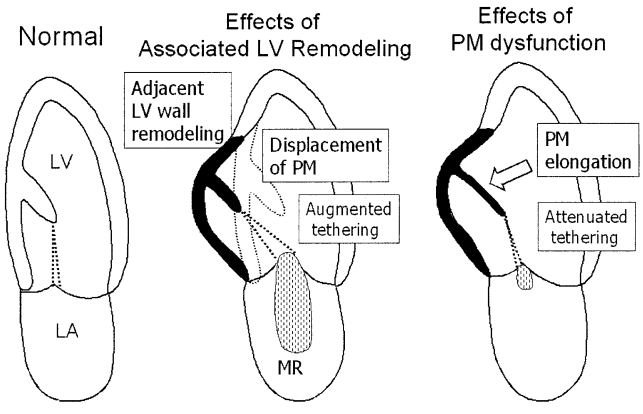

Figure 1. Expected potential and opposing effects of papillary muscle (PM) dysfunction resulting in exaggeration or attenuation of leaflet tethering and mitral regurgitation (MR). **(Middle panel)** Remodeling of the adjacent left ventricular (LV) wall, which accompanies PM dysfunction, causes outward displacement of the PM and thereby induces augmented leaflet tethering with MR. **(Right panel)** In the presence of adjacent LV wall remodeling, PM dysfunction per se results in systolic PM elongation or less shortening, which thus attenuates tethering and MR. LA = left atrium.

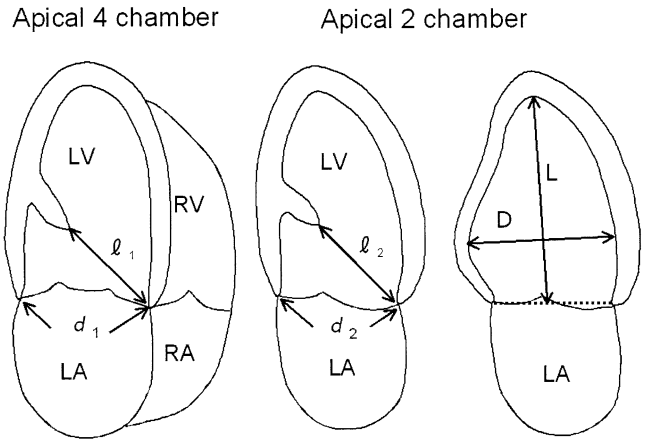

Figure 2. Quantitative measurements of the geometry of the left ventricle (LV) and mitral valve complex using two-dimensional echocardiography. D = short-axis dimension; d = mitral annular dimension; LA = left atrium; RA = right atrium; RV = right ventricle; L = long-axis dimension; ℓ_1 = lateral papillary muscle (PM) tethering distance; ℓ_2 = medial PM tethering distance.

Evaluation of PM function by 2D and Doppler echocardiography with tissue strain imaging. Papillary muscle systolic contraction generates tension in the chordae to maintain the systolic leaflet position or to prevent leaflet prolapse while the wall between the PM and mitral annulus contracts. Therefore, PM dysfunction was defined as PM contractile dysfunction in this study. Because PM contraction is spatially and temporally heterogeneous (27), PM dysfunction was further defined as peak systolic PM shortening in its long-axis direction or peak systolic PM thickening in its short-axis direction. Two methods were used to evaluate PM function. The end-diastolic and end-systolic medial or lateral PM width at its mid-portion was measured in the apical two- and four-chamber views to obtain systolic PM thickening by 2D echocardiography. Tissue Doppler imaging data was also recorded in these views to evaluate the medial and lateral PM longitudinal systolic strain (28).

Scanning was adjusted to achieve maximal alignment of the Doppler beam direction and the PM long axis, and each Doppler sample volume was manually placed frame-by-frame at the mid-portion of the PM. The strain rate profiles were averaged over three cardiac cycles and integrated over time to derive strain profiles using end-diastole as the reference point, and PM peak systolic strain was then measured (Fig. 3).

Reproducibility of measurements. Two independent observers repeated 10 measurements of medial PM systolic thickening and the longitudinal peak systolic strain. Differences in these measurements were obtained to estimate interobserver variability. The same observer repeated the 10 measurements, and intraobserver variability was calculated.

Grouping of patients. Based on the degree of basal inferoposterior LV bulging, evaluated by the short-to-long axis dimension ratio (D/L) of LV in the mid-systolic apical two-chamber view (Fig. 2), the patients were divided into two groups: group 1 with significant LV bulging and a D/L >0.60 (upper normal value), and group 2 without significant LV bulging. Patients in group 1 were considered to have similar locations and extent of LV remodeling as judged by the presence of significant inferoposterior bulging and the absence of advanced bulging involving other territories.

Statistical analysis. Determinants of the MR fraction were initially identified by linear or curvilinear univariate analysis. Stepwise multiple linear regression analysis was then performed, entering variables with significant relationships to the MR fraction by univariate analysis. A p value <0.05 was considered significant.

RESULTS

Patient profile. Compared to the patients in group 2, those in group 1 had a significantly higher incidence of congestive heart failure, a larger LV EDV, a greater reduction in LV EF, a more spherical LV, a dilated mitral annulus, longer PM tethering distances, more impaired medial PM function, and greater MR (Table 1).

Relationships between PM tethering or function and MR in all subjects irrespective of remodeling. The MR fraction showed significant correlations with several indexes describing the mitral valve apparatus, including LV sphericity, MAA, and medial PM tethering distance (Table 2). There was no significant relationship between PM dysfunction based on systolic thickening or longitudinal strain and the MR fraction, indicating that ischemic MR has no consistent relationship with PM dysfunction in patients with variable degrees of inferoposterior LV remodeling. Multiple regression analysis identified an increased medial PM tethering distance as the only independent determinant of the MR fraction.

Relationships between PM tethering or function and MR in group 1. The MR fraction was significantly correlated with multiple indexes describing the mitral valve apparatus, including the MAA, medial PM tethering distance, medial PM systolic thickening, and systolic strain (Table 2). In contrast to the results in all of the subjects grouped together irrespective of remodeling, the MR fraction was significantly correlated with systolic thickening and longitudinal peak systolic strain of the medial PM (Fig. 4, Table 2), indicating that good PM function was associated with greater MR, and that PM dysfunction was associated with less MR in patients with LV remodeling of a similar location and extent (Fig. 4). Although there were no significant relationships between PM dysfunction and the PM tethering distance in all of the subjects grouped together, PM dysfunction was significantly correlated with tethering distance, indicating that PM dysfunction was associated with a shorter PM tethering distance in patients

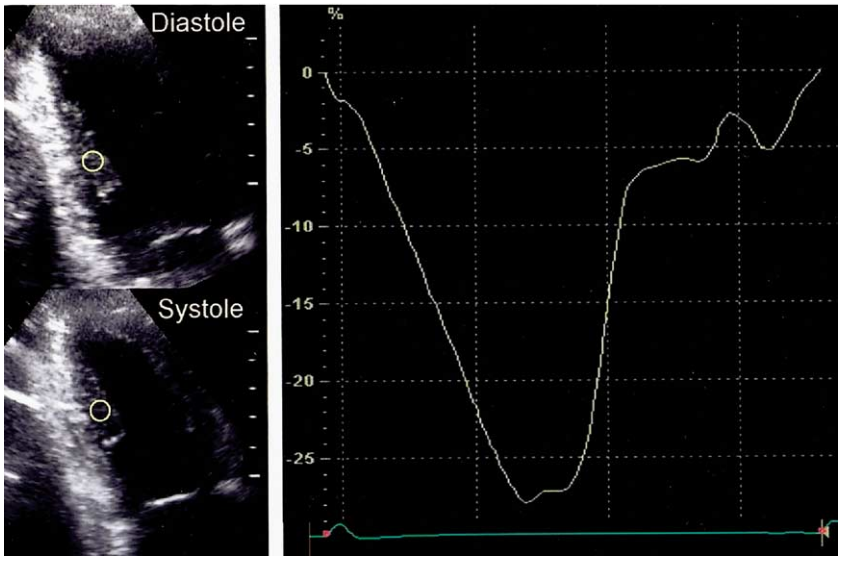

Figure 3. Methods used to evaluate papillary muscle (PM) function. Normal systolic PM thickening seen by two-dimensional echocardiography is shown in the **left upper and lower panels** and the **right panel** shows normal systolic PM longitudinal shortening as assessed by tissue strain imaging.

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Table 1. Patient Profile

	All Subjects (n = 40)	Group 1 (n = 29)	Group 2 (n = 11)	p Value
Age (yrs)	66.7 ± 7.8	68.1 ± 7.5	63.0 ± 7.3	NS
Male (%)	75	74	78	NS
Body mass index (kg/m^2)	1.61 ± 0.12	1.60 ± 0.12	1.63 ± 0.10	NS
Time since AMI (yrs)	4 ± 2	3 ± 2	4 ± 3	NS
CHF (%)	23	28	9	<0.01
Angina (%)	0	0	0	NS
LV EDVI (ml/m^2)	76 ± 15	82 ± 13	60 ± 6	<0.01
EF (%)	50 ± 8	48 ± 7	54 ± 7	<0.05
LV sphericity	0.64 ± 0.09	0.68 ± 0.06	0.53 ± 0.04	<0.01
MAA (cm^2/m^2)	4.7 ± 0.8	5.0 ± 0.7	4.1 ± 0.6	<0.01
Medial PM tethering distance (mm/m^2)	22.6 ± 2.7	23.3 ± 2.6	20.5 ± 1.8	<0.01
Lateral PM tethering distance (mm/m^2)	21.2 ± 2.6	21.8 ± 2.6	19.7 ± 1.8	<0.05
Medial PM systolic thickening (%)	14 ± 13	13 ± 14	17 ± 7	<0.05
Lateral PM systolic thickening (%)	19 ± 10	20 ± 11	19 ± 9	NS
Medial PM peak systolic strain (%)	−11 ± 11	−9 ± 12	−15 ± 6	<0.05
Lateral PM peak systolic strain (%)	−18 ± 4	−17 ± 4	−19 ± 3	NS
MR fraction (%)	19 ± 14	24 ± 13	7 ± 5	<0.01

AMI = acute myocardial infarction; CHF = congestive heart failure; EDVI = end-diastolic volume index; EF = ejection fraction; LV = left ventricular; MAA = mitral annular area; MR = mitral regurgitation; PM = papillary muscle.

with LV remodeling of a similar location and extent (PM strain: r = 0.43, p = 0.02; PM thickening: r = 0.39, p = 0.04). The loss of a significant relationship for LV sphericity in the univariate analysis in group 1 suggests that patients in this group have similar LV remodeling. Multivariate analysis similarly identified an increased medial PM tethering distance as the only independent determinant of the MR fraction. Figures 5 and 6 show data from representative patients with discrepant findings between PM function and MR but with consistent findings between PM tethering and MR.

Reproducibility of measurements. The inter- and intraobserver variabilities for measurements of %PM thickening and peak systolic strain were 2.4 ± 2.5% and 2.0 ± 1.3% or 2.9 ± 2.2% and 2.4 ± 1.6%, respectively.

DISCUSSION

Our study demonstrated that PM dysfunction does not have a significant relationship with MR fraction in patients with a prior inferior MI. This may be due to superimposing two opposing effects, one effect from adjacent LV wall remodeling that exaggerates tethering and MR, and the other effect from PM dysfunction with less PM longitudinal shortening that attenuates the tethering and MR. These

Table 2. Determinants of the MR Fraction

	Univariate		Multivariate
	r^2	p Value	p Value
All subjects			
LV EDVI (ml/m^2)	0.11	NS	N/A
EF (%)	0.01	NS	N/A
LV sphericity	0.34	<0.001	NS
MAA (cm^2/m^2)	0.44	<0.001	NS
Medial PM tethering distance (mm/m^2)	0.64	<0.001	<0.001
Lateral PM tethering distance (mm/m^2)	0.13	NS	N/A
Medial PM systolic thickening (%)	0.05	NS	N/A
Lateral PM systolic thickening (%)	0.01	NS	N/A
Medial PM peak systolic strain (%)	0.10	NS	N/A
Lateral PM peak systolic strain (%)	0.03	NS	N/A
Group 1 with significant and comparable LV remodeling			
LV EDVI (ml/m^2)	0.01	NS	N/A
EF (%)	0.03	NS	N/A
LV sphericity	0.09	NS	N/A
MAA (cm^2/m^2)	0.31	<0.01	NS
Medial PM tethering distance (mm/m^2)	0.59	<0.001	<0.001
Lateral PM tethering distance (mm/m^2)	0.10	NS	N/A
Medial PM systolic thickening (%)	0.20	0.01	NS
Lateral PM systolic thickening (%)	0.01	NS	N/A
Medial PM peak systolic strain (%)	0.33	<0.01	NS
Lateral PM peak systolic strain (%)	0.01	NS	N/A

EDVI = end-diastolic volume index; EF = ejection fraction; LV = left ventricular; MAA = mitral annular area; PM = papillary muscle.

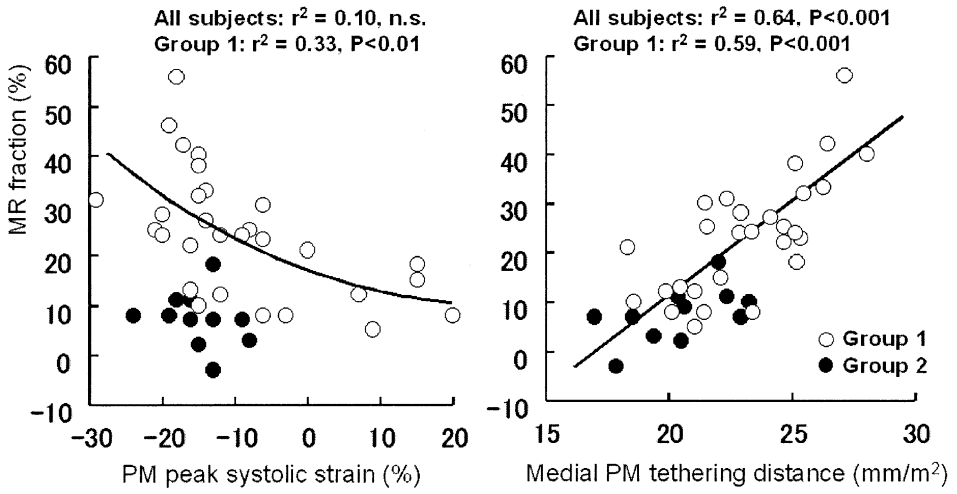

Figure 4. Scatter plots showing the relationships between the mitral regurgitation (MR) fraction and medial papillary muscle (PM) peak systolic strain **(left panel)** or medial PM tethering distance **(right panel)**. The MR fraction was significantly correlated with the medial PM tethering distance in all of the subjects taken together and those in group 1. While the MR fraction did not show a significant correlation with the PM systolic strain in all of the subjects with variable degrees of associated left ventricular (LV) remodeling, there was a significant correlation in group 1 patients with LV remodeling of a similar location and extent.

effects are clinically difficult to distinguish. However, PM dysfunction is significantly and inversely correlated with the MR fraction and tethering distance in selected patients with LV remodeling of a similar location and extent due to prior inferior MI, potentially due to the disappearance of individual variability in the effects of adjacent LV wall remodeling. This may allow one to evaluate the effects of PM dysfunction on mitral valve function under approximately comparable effects of adjacent LV wall remodeling. In the presence of adjacent wall remodeling, normal or impaired PM contraction may augment or attenuate tethering, respectively, supporting the hypothesis of the current study. The medial PM tethering distance was the major determinant of ischemic MR in all of the patients taken together and also in selected patients with inferior MI in the present study. In addition, PM dysfunction was not an independent determinant of MR by multivariate analysis, even in group 1. These findings suggest that the PM tethering distance is the final determinant of MR, and PM dysfunction is one of the determinants of the tethering distance along with LV remodeling.

Relationship to previous studies. Although experimental studies have demonstrated that isolated PM dysfunction does not cause significant ischemic MR (6–9), the term "PM dysfunction syndrome" has been frequently used in clinical practice, potentially due to the complexity of the mechanism of ischemic MR and the difficulty in evaluating PM function in clinical patients. Recent advances in echo-

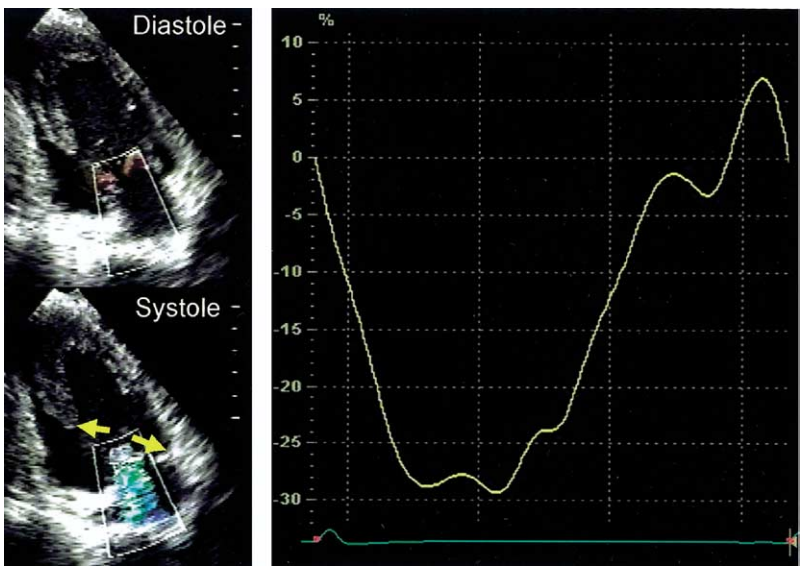

Figure 5. A patient with significant ischemic mitral regurgitation (MR) despite good papillary muscle (PM) function shown by normal systolic PM thickening on two-dimensional echocardiography **(left upper and lower panels)** and normal systolic PM longitudinal shortening with strain imaging **(right panel)**. The medial PM tethering distance **(arrows)** is long and can explain the MR.

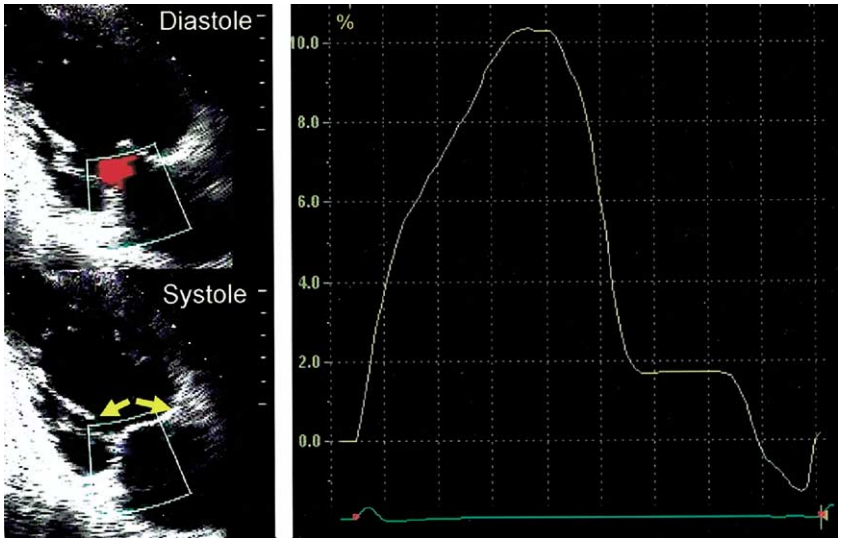

Figure 6. A patient with trace mitral regurgitation (MR) despite poor papillary muscle (PM) function shown by absent systolic PM thickening on two-dimensional echocardiography **(left upper and lower panels)** and systolic PM longitudinal elongation as assessed by strain imaging **(right panel)**. The medial PM tethering distance **(arrows)** is normal and can explain the lack of significant MR.

cardiography using tissue Doppler strain imaging have enabled the evaluation of regional myocardial function (29), which can be applied to the PM (28). Papillary muscle dysfunction, evaluated by 2D echocardiography and tissue Doppler strain imaging, attenuated ischemic MR in selected patients with LV remodeling of a similar location and extent due to prior inferior MI in the present study. The results are consistent with a previous animal study by Messas et al. (28), which demonstrated that PM dysfunction attenuates leaflet tethering and ischemic MR. The current study further demonstrated that PM dysfunction attenuates ischemic MR in patients with similar degrees of inferoposterior LV remodeling.

Clinical applications. The results of the study suggest a central role of leaflet tethering (10–21), as opposed to PM dysfunction, in the mechanism responsible for ischemic MR. Therapeutic approaches to relieve ischemic MR need to be targeted to reduce tethering by LV remodeling. Revascularization of the viable adjacent LV wall is expected to relieve ischemic MR (30). The results also support surgical approaches targeted at relieving tethering by aneurysm plication and repositioning of PMs (31–34). In addition, our results suggest that the term "PM dysfunction" be changed to "PM displacement" to better describe ischemic MR.

Study limitations. Ischemic MR includes a wide spectrum of underlying pathophysiologies, such as acute or chronic and global or segmental LV remodeling (6–21,35). The present study only addressed ischemic MR due to chronic inferoposterior MI, and found an inverse relationship between PM dysfunction and the degree of MR. Although PM dysfunction with reduced systolic longitudinal shortening, in theory, is expected to attenuate tethering and MR in general patients with ischemic MR, such an inverse relationship may not be relevant in many patients with ischemic MR due to different pathophysiologies, such as dilated/ischemic cardiomyopathy, anteroseptal MI, and other entities with only modest variability in PM dysfunction and more extensive LV remodeling. Medial PM displacement was evaluated by determining PM tethering length by 2D echocardiography. Therefore, anteroposterior, mediolateral, and basoapical displacements of the PM were not evaluated (13–21). Because PM contraction varies according to the spatial direction (36), it is necessary to attempt to establish a standardized angle used for echocardiographic evaluation of PM strain and to carefully interpret the derived data. Cardiac phase-to-phase variability of normal PM contraction, with no contraction during the isovolumic periods and shortening in the ejection time, and variability of ischemic PM contraction, with lengthening in the isovolumic contraction time to ejection time and shortening during the isovolumic relaxation time, have been demonstrated (27). Furthermore, the degree of ischemic MR also varies according to the cardiac cycle, usually with maximal regurgitation occurring in the isovolumic phases (37). The relationship between phasic variability in PM contraction and the variability in MR remains unknown. Nevertheless, the purpose of this study was achieved by demonstrating that ischemic MR is attenuated by PM dysfunction per se and is related to geometric changes in the mitral valve apparatus with displacement of the medial PM in patients with inferior MI.

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