Valvular Heart Disease

Mitral Regurgitation After Anteroapical Myocardial Infarction
New Mechanistic Insights

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Background—Mitral regurgitation (MR) generally accompanies inferobasal myocardial infarction (MI), with leaflet tethering by displaced papillary muscles. Mitral regurgitation is also reported with anteroapical MI without global dilatation or inferior wall motion abnormalities. We hypothesized that anteroapical MI extending to the inferior apex displaces the papillary muscles, tethering the mitral leaflets to cause MR.

Methods and Results—In the retrospective part of the study, consecutive anteroapical MI patients were studied. Moderate-severe MR occurred in 9% of 234 patients with only anteroapical MI versus 17% of 242 with inferoapical extension (P<0.001). Ejection fraction was only mildly different (41±4% versus 46±5%; P<0.01). In the human mechanistic portion of the study, 60 anteroapical MI patients (20 with only 2 apical segments involved and 40 with involvement of all 4 apical segments; 20 with MR and 20 without MR) were compared with 20 normal controls. Those with MR (≥moderate) had higher systolic papillary muscle–to-annulus tethering length (P<0.01). Mitral regurgitation grade correlated most strongly with tethering length (r=0.70) and its diminished systolic shortening (r=−0.65). In the animal study, 9 sheep with left anterior descending coronary artery ligation were analyzed. Four sheep that developed MR had inferoapical MI extension with tethering length increasing over 1.5 months (2.1±0.4 to 2.9±0.4 cm, P<0.001) versus no significant increase in 5 sheep without MR (2.0±0.4 to 2.1±0.3 cm, P not statistically significant). In MR sheep, the normal decrease in tethering length from diastole to systole was eliminated (P<0.01).

Conclusions—Anteroapical MI with inferoapical extension can mechanically displace papillary muscles, causing MR despite the absence of basal and midinferior wall motion abnormalities. This suggests the possibility of repositioning treatments for this condition. (Circulation. 2011;123:1529-1536.)

Key Words: ischemia • mitral regurgitation • anterior wall myocardial infarction • echocardiography, three-dimensional • remodeling

Ischemic mitral regurgitation (MR) is a common complication of myocardial infarction (MI)1–12 that adversely influences prognosis.13–16 Treatment remains frustrating, but new approaches have been suggested based on improved understanding of mechanism that focuses on ventricular changes displacing the mitral leaflet attachments at the papillary muscle (PM) and annular level, restricting mitral leaflet closure.7,8 This pattern has generally been associated with 2 scenarios: infarction and bulging of the inferior and posterior left ventricular (LV) base and midventricle underlying the PMs1–12 and global LV dilatation and dysfunction, which also involves the PMs and annulus.7,8

Clinical Perspective on p 1536

Clinical studies, however, implicate not only segmental inferobasal but also anteroapical MIs in the pathogenesis of MR and its prognostic impact,14,15 raising the question of why MR occurs in such infarctions. We can propose that anterior infarct extension to the inferior apex can lead to bulging of the dilated apex, which mechanically displaces or tethers one or both PMs toward the apex, even though the muscle underlying the PM base is not infarcted.17 This would in turn lead to mitral leaflet tethering and MR (Figure 1).

The present study therefore tested the hypothesis that apical wall motion abnormality without involvement of the inferior or posterior base or midventricle can cause MR with relatively preserved global LV size and systolic function. The putative mechanism is increased mitral leaflet tethering exerted by the apex. This was first tested by a retrospective clinical analysis to confirm that important MR is more frequent in patients with anteroapical MIs in whom the inferior apex is also involved. A detailed quantitative analysis
of tethering mechanism was then performed in patients with anteroapical MI, comparing those with and without MR. This mechanism was confirmed in a controlled experimental large-animal model of apical infarction.

**Methods**

**Human Retrospective Study**

The transthoracic cardiac ultrasound database at our institution was retrospectively searched over 3 years. We identified 476 patients with anteroapical MIs without involvement of the inferoapical leaflet closure pattern in the 2-dimensional (segment) infarction. Seg indicates segment; LV, left ventricle; Ant, anterior; LA, left atrium; and AO, aorta.

**Human Mechanistic Study**

Eighty patients were analyzed, divided into 4 groups (20 patients each):

- **Group 1:** MI involving all 4 apical segments with important (≥ moderate) MR
- **Group 2:** MI involving all 4 apical segments with no or minimal (< mild) MR
- **Group 3:** MI involving the anterior apical segments only, with no or minimal (< mild) MR
- **Group 4:** A normal control group of 20 consecutive patients with normal LV global and segmental function, with no evidence of other cardiac disease or MR by echocardiography or clinical records.

We tested the hypothesis that MR among all these patients is predicted by the tethering length (TL) from the PM tip to the anterior apical segments versus akinesis of all 4 apical segments, and the proportion with ≥ moderate MR in each group compared.

**Sheep Mechanistic Study**

The sheep mechanistic study was based on our observation that mid to distal occlusion of the left anterior descending coronary artery in sheep, which typically produces an anteroapical MI without MR, occasionally produces inferior apical involvement, as well, and in such instances can also produce MR with a typically restricted leaflet closure pattern in the absence of global LV dilatation and dysfunction (Ronen Beeri, MD, Chaim Yosef, MD, J. Luis Guerrero, BS, Roger J. Hajjar, MD, Robert A. Levine, MD, unpublished results). Dorsett hybrid sheep (20 to 30 kg) were loaded for 3 days with amiodarone (200 mg PO BID), then anesthetized with thiopentothal sodium (0.5 mL/kg), intubated, and ventilated at 15 mL/kg with a 2% isoflurane and oxygen mixture. All received 1 dose of glycopyrrolate (0.4 mg IV) and prophylactic vancomycin (0.5 g IV) and amiodarone (150 mg IV drip over the course of the operation). Surface ECG was monitored and a sterile left thoracotomy performed with pericardial incision and creation of a cradle. After baseline echo imaging, an anteroapical MI was produced by ligating the mid-to-distal left anterior descending coronary artery, known to produce a substantial MI. An immediate 2-dimensional echo apical image was performed to confirm that septal wall motion abnormality extends at least one third of the way from LV apex to base for standardization. Antibiotics (cephapirin, 0.5 gm IV) and analgesics (buprenorphine, 0.3 mg BID) were administered for the next 5 days, and oral amiodarone (200 mg BID) for the next 3. During repeat sterile thoracotomy at an average of 45 ± 7 days, 2-dimensional and 3-dimensional (3D) echo were performed to evaluate LV remodeling and function. The animal studies conformed to National Institutes of Health guidelines for animal research (Guide for the Care and Use of Laboratory Animals, National Research Council, Washington, DC, 1996) and were approved by the institutional animal care committee. We compared 5 such sheep that developed MR with 4 sheep having anteroapical MI without MR from comparable left anterior descending coronary artery ligations, measuring changes in the LV and mitral valve over an average of 45 days follow-up.

**Echocardiographic Methods**

In the patient studies, 2-dimensional echo studies with Doppler color flow mapping were performed in standard views using a Philips Sonos 7500 machine with an S3 transducer (Philips, Andover, MA). Depth and sector settings were optimized for color Doppler resolution and MR quantification. LV end-systolic and end-diastolic volumes (LVESV, LVEDV) and EF were calculated by the biplane method of discs. In the sheep, rotated apical images were obtained at 10° intervals with a 5 MHz TEE probe (Philips Sonos 7500) gated to ECG and respiration. Digital images were analyzed on a workstation with custom programs. Endocardial surfaces were traced to calculate LV volumes and EF using a validated technique. MR was initially graded semiquantitatively (0–4) on the basis of vena contracta dimension and jet area/left atrial area in the parasternal long axis and apical long-axis and 4-chamber views; MR assessment was later corroborated by quantitative Doppler assessment: Regurgitant volume was calculated as mitral inflow minus...
Statistical Analysis

The line connecting the annular hinge points (Figure 1).22 as the perpendicular from the tip of the inferior (medial) papillary PM to height (TH) was measured at end diastole and end systole in same view point. In the sheep studies, this TL was measured to the medial fibrous annular dimension, systolic and diastolic TLs and their difference. In the human and sheep studies, multiple linear regression analysis was performed to determine the contribution of LV and mitral valve inflow volume, and verified to be 7% in patients and sheep with trace or no MR by semiquantitative assessment.21

Mitral Valve Relationships

In the mechanistic patient studies, TL was measured at end diastole (initial mitral valve closure) and end systole (smallest LV cavity just before mitral valve opening) in the apical long-axis view (Figure 1) from the tip of the inferior (medial) PM to the anterior mitral annular hinge point. In the sheep studies, this TL was measured to the medial fibrous trigone on the basis of tracings in the rotated 3D apical views. Tethering height (TH) was measured at end diastole and end systole in same view as the perpendicular from the tip of the inferior (medial) papillary PM to the line connecting the annular hinge points (Figure 1).22

Statistical Analysis

Data are presented as mean±SD. Data analysis was performed using SPSS (Chicago, IL). Variables were compared among patient and animal groups by analysis of variance, with 2-way t tests among groups when positive, using the Bonferroni correction. Changes in sheep studies from baseline (pre-MI) to follow-up were compared within animal groups by analysis of variance, with 2-way tests among groups by paired t test. In each of the mechanistic human and sheep studies, multiple linear regression analysis was performed to determine the contribution of LV and mitral valve measures to MR grade (in the sheep, presence or absence of important MR), entering LVEVS, LVEDV, EF, heart rate, maximal and minimal annular dimension, systolic and diastolic TLs and their difference. In the human and sheep mechanistic studies (studies 2 and 3), we dichotomized MR (no-to-minimal versus moderate-to-severe) and thus used binary logistic regression. All computations were done using SAS statistical software, version 9.12, SAS Institute Inc, Cary, NC. The variables most closely related to MR severity were identified by significance in binary logistic regression, entering LVEVS, LVEDV, EF, heart rate, maximal and minimal annular dimension, systolic and diastolic TLs, and their difference. Then, to ascertain the relative contribution of the significant variables to MR severity we used multivariate binary logistic regression, and derived the receiver operating characteristic (ROC) curves. The area under the ROC curve was estimated for each step of the multivariate analysis.

Results

Human Retrospective Study

Of the 476 patients identified after anterior MI without involvement of the inferoposterior base or midventricle, 234 (49%) had anterior MI involving the 2 anteroapical segments and 242 (51%) had involvement of all 4 apical segments. There was no significant difference between the groups in age (64±20 versus 63±15 years), gender (39% versus 49% women), body surface area (BSA; 1.78±0.21 versus 1.74±0.24 m²), time after MI (1.6±0.2 versus 1.7±0.5 months), or cardiovascular risk factor profile: diabetes mellitus (32.8% versus 33.1%), smoking (41% versus 43%), dyslipidemia (39% versus 37%), and hypertension (43% versus 39%). There was no significant difference between the groups in blood pressure (125±20/76±9 mm Hg versus 126±19/76±8 mm Hg) or heart rate (75±17 versus 74±18 bpm). LVEF was higher in the 2-segment group (46±5% versus 41±4%, P<0.01). The group with 4 segments involved had a significantly higher MR grade (1.9±0.8 versus 1.5±0.8, P<0.01). Moderate-to-severe MR (grades 3 to 4) occurred nearly twice as often in the 4-segment group (17±2% versus 9±2%, P<0.01).
Human Mechanistic Study

There were no significant differences in age, gender, or BSA among all the groups (Tables 1 and 2). Within the MI groups, there were no significant differences in time after MI, blood pressure, heart rate, or cardiovascular risk factor profile. Patients with 4-segment involvement and MR (group 1) demonstrated apical leaflet tethering with bulging dyskinesis of the inferior apical wall despite maintained thickening of the basal and midventricular LV wall (double-headed arrows, Figure 2A and B) accompanied by MR through the tethered leaflets (Figure 2C). The PM tip was visibly retracted toward the bulging inferior apex, exceeding its normal apical excursion. Quantitatively this corresponded to an important increase in systolic TL (4.1±0.6 cm versus 3.3±0.4 cm in group 2 with MI involving 4 segments with no MR, and also versus 3.1±0.1 cm in group 3 with MI involving the anterior apical segments only and 3.01±0.2 cm in the control group, P<0.01). Diastolic TL was also increased only in group 1 with inferoapical dyskinesis. The normal systolic decrease in TL accompanying ventricular emptying was virtually eliminated in group 1 with 4 apical segment involvement and MR, consistent with systolic retraction of the PM tip away from the annulus (Figure 3), but preserved in group 2 with 4 apical segment involvement without MR, whose members had no inferoapical dyskinesis, and in the 2 apical segment group with no or minimal MR.

TH, the component of TL parallel to the LV long axis and perpendicular to the annulus, was also higher in the MR group in systole and diastole, with a blunted systolic decrease. LVEF was lower in group 1 with 4 segment involvement and MR than in group 2 with 4 segment involvement without MR (35.7±6.5% versus 38.4±4.6%, P<0.01), who in turn had a lower EF than the 2 segment group (42.9±7.6%, P<0.01). The same trends were seen for LV volumes, which were largest in patients with 4 segments and MR (P<0.01, Table 2).

Binary logistic regression analysis showed that the presence of moderate or greater MR was predicted by TL and its systolic change, with ROC contributions (area under the ROC curve) of 0.74 and 0.71, respectively, with no significant contributions from LVEF, LV volume, or annular size.

Sheep Mechanistic Study

As in the human mechanistic study, animals that developed MR showed preserved thickening of the inferoposterior wall at the base and midventricle with dyskinesis of the anterior and inferior apex (Figure 4) and prominent systolic apical retraction of the PM tip, compared with only anteroapical bulging in the animals without MR (Table 3). In the sheep who developed MR, the average regurgitant volume was 15.4±1.5 mL and the average regurgitant fraction was 28.8±4.5% (moderate). There were no significant differences...
in the baseline characteristics of both groups, including LVESV, LVEDV, LVEF, heart rate, LV end-systolic and end-diastolic diameter at the base, mitral annular dimensions, or systolic and diastolic TLs. In both groups, the LV remodeled to a comparable extent over 45/7 days, with no significant differences in LV volumes at follow-up and a lower but not significantly decreased EF in the MR group (42.6±5.2 versus 47.4±5.3%, P=not significant). Systolic TL increased to a significantly greater extent over time in the MR group (by 0.8 versus 0.1 cm, P<0.001, Figure 5A). At follow-up, the normal systolic shortening of TL was virtually eliminated in the MR group, consistent with systolic PM retraction toward the apex (Figure 5B). The same changes pertained to TH. Logistic regression analysis showed that the presence of moderate or greater MR was predicted by systolic TL (area under the ROC curve=0.62), without significant contributions from LV volume, EF, or annular dimensions.

Discussion

Incomplete mitral leaflet closure with apically restricted leaflet coaptation is the final common pattern of ischemic or functional MR in LV dysfunction, with increased TL from an affected PM to the opposite mitral annulus being its strongest predictor in a variety of clinical and experimental settings. Until now, in the absence of global LV dysfunction and dilatation, it has widely been considered to result from contractile abnormalities localized to the inferoposterior LV base and midventricle; it has the potential, in turn, to exacerbate LV remodeling in a vicious cycle of MR increasing MR. This study demonstrates that PM displacement caused by the mechanical influence of an adjacent bulging apex, with dyskinesis extending from the anterior to the inferior apical wall, can also

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*MR group, after vs before MI, P<0.01; †Control group, after vs before MI, P<0.01; ‡MR vs control, after vs before MI, P<0.01.

Abbreviations as in Table 2.
create incomplete mitral leaflet closure and MR. MR in this setting also correlates best with systolic TL from PM tip to annulus, and the normal decrease in TL as ventricular cavity size decreases in systole is blunted or lost because of apical PM retraction. This mechanism is well illustrated by 3D endocardial reconstruction from a more recent patient with moderate ischemic MR despite evident contraction of the inferior base and midventricle (Figure 6, left, comparing the end-systolic cavity with the end-diastolic mesh) but with bulging dyskinesis of the apex, including its inferior segments.

This study was motivated by clinical and experimental observations that led to quantitative studies of mechanism, after a database review confirmed the higher frequency of moderate to severe MR in patients with anterior apical involvement. The mechanistic studies confirmed the relationships among MR, TL, and its dynamics, and also showed by 3D echocardiography that these changes evolve over time from a normal baseline in a controlled experimental model.

**Mechanistic Implications and Correlates**

These results further confirm that MR does not result from PM dysfunction alone, or even dysfunction of the myocardium underlying a PM, but rather, PM tip position relative to the mitral annulus. This confirms the mechanistic postulate of Sabbah et al. that distortions in LV shape, as opposed to nonspecific increases in volume or decreases in EF, play a central role in displacing the PM and disrupting coaptation. The comparison of patients with and without MR despite involvement of the same 4 apical segments is particularly instructive: MR was determined by inferoapical dyskinesis, increasing TL and decreasing its systolic shortening in the patients with MR.
In this context, important MR developed despite relatively preserved LV size and function, and the contribution of LVEF to MR was modest. Although patients with 4-segment apical involvement would be expected to have greater LV remodeling, that is not well represented by the gross global measures of LV volume and EF but is expressed by geometric changes in TL in systole and diastole that reflect localized apical remodeling. This further confirms the strong relationship between ischemic MR and localized LV remodeling, also seen with inferobasal MI, as well as the particular predisposition of the apex to remodel, as reported by Picard et al.\textsuperscript{25}

Clinical Implications

The current study expands our understanding of the spectrum of location, chronicity, and severity of LV dysfunction underlying ischemic MR; it may emphasize the contribution of ischemic MR to adverse prognosis even in patients with anterior MI independent of global LV dysfunction. This mechanism has practical implications because localized change should be susceptible to localized geometric treatments, by analogy to observations with infarctions at the base of the heart in which an adjustable localized patch, or polymer injection, can be titrated to eliminate ischemic MR.\textsuperscript{26,27} Our findings can also be considered in decisions on the potential benefit of revascularization in acute anteropapillary infarction. A strong theme in the surgical literature on LV reconstruction has been the influence of apical aneurysm repair on concomitant MR. Mickleborough’s group, for example, has shown that a modified linear closure excision repair of dyskinetic or akinetic LV aneurysms provides symptomatic relief of heart failure and good long-term survival, improves LV function, and decreases MR, which is a strong predictor of mortality, in 57% of patients imaged by ultrasound.\textsuperscript{28} The procedure realigns the PMs in order to reduce MR, as do reconstructive approaches of Kron and Menicanti and colleagues.\textsuperscript{29,30} Approaches that may benefit patients with more limited apical expansion causing MR may include limiting LV size or tethering with increased apical pericardial restraint, with myoplasty to wrap skeletal muscle around the apex, with infarct plication or apical bulging excision to reduce tethering force,\textsuperscript{31} or with leaflet or chordal elongation or modification.\textsuperscript{42}

Limitations and Future Directions

The clinical spectrum of ischemic MR is varied, and although this study explores 1 component of that spectrum not previously recognized, it importantly increases our understanding of common themes and potential therapeutic targets. This study is retrospective in nature and aims to describe the mechanism of this phenomenon rather than to assess its prevalence. Its existence suggests that it should be addressed when new therapies are formulated.

Conclusions

Anterior MI with dyskinetic inferopapillary extension can mechanically displace the PMs as an expression of localized LV remodeling, causing ischemic MR in the absence of prominent global LV dysfunction or dilatation or of typical inferobasal abnormalities. This suggests the possibility of repositioning treatments for this condition.

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Disclosures

None.

References

Ischemic mitral regurgitation (MR), which increases postinfarction heart failure and mortality, reflects mitral leaflet tethering by displaced papillary muscles. Until now, in the absence of global left ventricular dysfunction and dilatation, it has been considered to result from contractile abnormalities and wall bulging localized to the inferoposterior left ventricular base and midventricle. This clinical and experimental study demonstrates that ischemic MR can also be caused by localized left ventricular apical remodeling despite normal inferior wall contraction at the base and midventricle. Inferoapical dyskinesis can mechanically displace the papillary muscles and in turn tether the leaflets and create ischemic MR. Mitral regurgitation in this setting correlates best with increased systolic tethering length from the papillary muscle tip to the annulus, and the normal systolic decrease in tethering length is blunted or lost because of papillary muscle retraction toward the apex. This expands our understanding of the spectrum of left ventricular dysfunction causing ischemic MR and highlights the role of localized remodeling. This mechanism has practical implications for the possibility of localized repositioning and reconstructive treatments.
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