Paradoxic Decrease in Ischemic Mitral Regurgitation With Papillary Muscle Dysfunction
Insights From Three-Dimensional and Contrast Echocardiography With Strain Rate Measurement

Emmanuel Messas, MD, MSc; J. Luis Guerrero, BS; Mark D. Handschumacher, BS; Chi-Ming Chow, MD; Suzanne Sullivan, BS; Ehud Schwammenthal, MD, PhD; Robert A. Levine, MD

Background—Ischemic mitral regurgitation (MR) was first ascribed to papillary muscle (PM) contractile dysfunction. Current theories include apical leaflet tethering caused by left ventricular (LV) distortion, but PM dysfunction is still postulated and commonly diagnosed. PM contraction, however, parallels apical tethering, suggesting the hypothesis that PM contractile dysfunction can actually diminish MR due to ischemic distortion of the inferior base alone.

Methods and Results—We therefore occluded the proximal circumflex circulation in 7 sheep while maintaining PM perfusion, confirmed by contrast echocardiography. By 3D echocardiography, we measured the tethering distance between the ischemic medial PM tip and anterior annulus and LV ejection volume to give MR (by subtracting flowmeter LV outflow). In 6 sheep without initial MR, inferior ischemia alone produced PM tip retraction with restricted leaflet closure and mild-to-moderate MR (regurgitant fraction, 25.2±0.2 vs 8.0±0.3 mL; 3.8±0.5 mm to −2.2±0.7 mm axially relative to baseline; P<0.001) as PM strain rate decreased from 0.78±0.07 per second (contraction) to 0.42±0.06 per second (elongation, P<0.001) and leaflet tenting decreased. In one sheep, prolapse and MR resolved with inferior ischemia and recurred with PM ischemia.

Conclusions—PM contractile dysfunction can paradoxically decrease MR from inferobasal ischemia by reducing leaflet tethering to improve coaptation. This emphasizes the role of geometric factors in ischemic MR mechanism and potential therapy. (Circulation. 2001;104:1952-1957.)

Key Words: mitral valve • regurgitation • remodeling • myocardial infarction • echocardiography

Mitral regurgitation (MR) is a common complication of ischemic heart disease and myocardial infarction, doubling the risk of late death.1,2 Since its initial recognition by Burch and De Pasquale,3–5 ischemic MR has been attributed, in both name and mechanism, to dysfunction of the papillary muscles (PMs), impairing their normal support of effective coaptation.3–7 Early experimental studies refined this concept by suggesting that to produce important MR required damaging not only the PMs but also the underlying myocardium8–11; MR, however, also frequently developed in the chronic phase of ethanol injection into the PMs.8 More recently, Kisanuki et al7 showed that patients with diminished PM shortening had the most severe MR, perpetuating the term “PM dysfunction,” which remains common in clinical parlance and echocardiographic interpretation. The goal of this study is to reassess the role of PM dysfunction in ischemic MR.

Prevailing explanations for such MR have focused on two factors: (1) ischemic distortion of ventricular geometry, displacing the attachments of the mitral leaflets to the PMs and annulus and restricting their ability to close effectively at the annular level,12–19 and (2) decreased left ventricular (LV)-generated force acting to close the leaflets,11 particularly when they are under increased tension.18 Both factors would produce the apically tented or tethered leaflet configuration referred to as incomplete mitral leaflet closure.6 Nevertheless, a potential contributory role of PM contractile dysfunction has remained within the range of proposed mechanisms. This persistent notion is particularly problematic when we consider the following reasoning: If, in fact,
ischemic MR results from a net imbalance of apically directed forces—increased tethering and diminished LV contraction—then normal PM contraction, which is also directed toward the apex, should in principle increase apical tethering and augment MR. Conversely, we can propose the hypothesis that in the presence of MR caused by increased tethering, for example, from ischemia with outward distortion of the inferior base of the heart (but not involving the PMs), adding contractile dysfunction of the PMs can paradoxically diminish MR by allowing the leaflets to seat better and approach the annular level more closely. Tethering may also be reduced by possible stretching of the ischemic papillary muscle toward the annulus by LV force transmitted through the leaflets and chords (Figure 1). Testing this hypothesis is important not only to sharpen our understanding of mechanism but also practically because abnormal tethering can potentially be addressed mechanically,1,2,20 but restoring PM contractile function may not be possible.

We tested this hypothesis in an experimental model that allows us to separate ischemic dysfunction of the PMs from that of the inferoposterior wall between the insertion of the PMs and the mitral annulus. Three-dimensional echocardiography was used to quantify the relations between components of the mitral apparatus; contrast echocardiography to confirm PM perfusion; and Doppler strain rate to measure longitudinal PM contraction noninvasively, without PM instrumentation.

Methods

Experimental Model

To separate ischemia and perfusion of the inferoposterior base from that of the more apically positioned PMs, we used a technique similar to the salvage perfusion used in angioplasty. The aim was to infarct a proximal (basal) portion of the left circumflex (LCX) coronary artery territory while maintaining perfusion of the more distal (apical) papillary muscles. An 8F wide-bore cannula was advanced from the left carotid artery to the ostium of the left main coronary artery, and a smaller 6F perfusion catheter was inserted through it with its tip placed within the circumflex, just before the origin of the second obtuse marginal branch (Figure I; can be found Online at http://www.circulationaha.org); the guiding catheter was then withdrawn. The perfusion catheter had a side-hole entry port at the aortic root level. Therefore, ligatures could be placed around the proximal LCX, near its origin and before the second obtuse marginal, to produce ischemia of the anterior PM and the septum still contract in this sheep model,16 unlike more extensive changes that can develop in the dog.13

Protocol

This approach was applied in 7 Dorsett hybrid sheep anesthetized with thiopental (0.5 mL/kg), intubated, and ventilated at 15 mL/kg with 2% isoflurane and oxygen and given glycopyrrolate (0.4 mg IV), with procainamide (15 mg/kg IV) and lidocaine (3 mg/kg IV followed by 2 mg/min) infused 10 minutes before coronary ligature.

After left thoracotomy and pericardial incision were performed, hemodynamic monitoring devices were inserted (left atrial [LA] and LV Millar catheters and aortic root Transonic flow probe). After baseline imaging and hemodynamic measurements were performed, including assessment of PM contraction (see below), the PM perfusion catheter was placed and the proximal LCX ligatures were tied to produce ischemia of the inferior base; after 30 minutes (the typical time for wall distortion and ischemic MR to develop), imaging and hemodynamics were repeated, and PM perfusion was confirmed by contrast echocardiography (see below). In the final stage, the proximal LCX ligatures were closed and the perfusion catheter was removed, producing combined inferior and PM ischemia.

Three-Dimensional Echocardiography

Thirty rotated LV apical views were acquired (5 MHz, epicardial, Agilent Sonos 5500) with suspended respiration as previously described and validated against sonomicrometry.17 Three-dimensional LV volumes were obtained through endocardial borders from 9 views.21 MR stroke volume was calculated as LV ejection volume minus aortic outflow volume directly measured by flowmeter,22 and MR orifice area was calculated from regurgitant stroke...
Hemodynamic and geometric measures were compared among stages and sheep by 2-way ANOVA. Significant ANOVAs were explored by 2 paired t tests (inferobasal ischemia versus baseline and versus combined inferior and PM ischemia), with significance at P<0.01 (Bonferroni-corrected).

Results

Mitrail Regurgitation

Six of the 7 sheep studied had no or only trace MR at baseline and are analyzed together; the seventh had mitral valve prolapse and moderate MR at baseline and was studied with the same protocol but reported separately.

In the 6 sheep without baseline prolapse, ischemia of the inferior base alone with preserved PM perfusion outwardly distorted the affected wall, retracting the PM tip away from the annulus and causing apical tenting of the mitral leaflets with mild to moderate MR (Figure 4). In all animals studied, adding PM ischemia consistently decreased the MR despite greater degrees of LV systolic dysfunction and annular dilation (Table). Images showed improved seating of the leaflets at the annular level with PM ischemia; the inactivated medial PM appeared to elongate, and its tip moved closer to the annulus, as quantified below. Although the MR driving pressure (=LV−LA pressure) trended toward lower values with the larger ischemic territory, the MR orifice area, which factors out the driving pressure, also decreased considerably with added PM ischemia. Moreover, MR stroke volume and orifice area decreased despite a trend (not significant) toward lower mitral valve closing force (=LVP−LAP)×mitral annular area.

Quantitative Geometric Analysis

The mid-systolic PM-to-anterior annular tethering length for the medial PM (its axial component, expressing the major effect of PM inactivation and loss of its longitudinal contraction) increased with ischemia limited to the inferobasal wall as that akinetic wall remodeled away from the anterior annulus, displacing the PM along with it. This value returned toward normal and actually decreased relative to baseline when PM ischemia was added and the apical vector of PM contraction was lost (Figure II; also see the Table). Moreover, there was a nonlinear relation between MR and tethering length, with a steeper rise in MR as tethering increased, suggesting that a normal excess of leaflet area is being used up (Figure II).

PM Assessment

Contrast echocardiography demonstrated preserved PM perfusion in the stage with inferobasal ischemia in all animals. Similarly, PM contraction was preserved in that stage but was lost in the final stage. The normal peak systolic strain rate corresponding to longitudinal PM contraction was 0.78±0.07 per second (average±SD in 5 beats) versus 0.75±0.03 per second with inferobasal ischemia but normal PM perfusion (no significant difference) and −0.42±0.06 per second with combined inferior and PM ischemia (P<0.001); this negative strain rate, indicating that the velocity of motion toward the apex is lower at the PM tip than at its insertion, corresponds to PM elongation.
Prolapse

In the sheep with posterior leaflet prolapse and significant baseline MR, inferobasal ischemia actually reduced MR, with an increase in tethering length retracting the leaflets into the LV and eliminating prolapse. With PM ischemia, prolapse and MR recurred in a pattern parallel to that observed in the other sheep, with PM ischemia normalizing the augmented tethering imposed on the leaflets by inferobasal remodeling (Figure III).

Discussion

After nearly 4 decades, ischemic MR in the absence of PM rupture is still widely referred to as PM dysfunction in both clinical and echocardiographic practice. Although the concept has been broadened to include ischemic ventricular distortion with displacement of the PMs along with their underlying myocardium, a role for PM contractile dysfunction is still supported by clinical and experimental observations.7,8 Such a role is difficult to test directly because contractile dysfunction of the PMs frequently accompanies geometric changes of their adjacent walls. The experimental model in this study effectively separates these two factors. The results show that ischemic distortion of the inferior wall restricts leaflet closure and causes MR but that adding PM contractile dysfunction actually decreases MR stroke volume and orifice area despite a larger ischemic territory. This results from normalization of the 3D tethering relations between the PM tips and mitral annulus.25 Normal PM contraction toward the apex acts to augment leaflet tethering; reducing PM contraction allows the leaflets to seat better at the annular level with less apical tenting and MR. The finding of a negative strain rate, indicating PM elongation that allows the PM tip to approach closer to the annulus, is consistent with Gam’s experimental observations that ischemic papillary muscles are elongated in situ by the force exerted on them through the mitral leaflets and chordae.26

Implications

Mechanistically, these results emphasize the central role of geometric changes and tethering in causing ischemic MR.27 Practically, they lend further support to therapeutic efforts directly targeting the fundamental tethering imbalance that restricts leaflet closure, either by plicating distorted infarct regions19,28 or by resecting myocardium between the PMs.1,29 Such interventions aim to overcome the variable, often frustrating results of annuloplasty techniques that only incompletely address tethering at the annular end.1,2,20,30 The benefit of preventing ischemic distortion can also be a factor in decisions regarding thrombolysis in acute inferior infarctions despite their often limited size.31 The results of this study can help us understand the dynamic relation between leaflets and ventricle, for example, the diminution of mitral valve prolapse in occasional patients whose left ventricles dilate,22 as in our seventh sheep. Finally, from a technical point of view, the terminology “PM dysfunction” as an explanation for ischemic MR with incomplete mitral leaflet closure or apical tenting in echocardiographic reports should be replaced with a term such as “PM displacement.”

Limitations and Prior Literature

The clinical spectrum of ischemic MR includes widely varying location and chronicity of ischemia, PM tip geometry, and
valve leaflets come into better apposition to persist regardless of PM inactivation.

more severe LV dilation and tethering, ischemic MR is likely diminished by PM contractile dysfunction. It is reasonable to suppose, however, that with more severe LV dilation and tethering, ischemic MR is likely to persist regardless of PM inactivation.

The study design precluded consistent histologic confirmation of ischemic zone because two stages (with and without PM perfusion) needed to be successively studied in the same animal. Contrast echocardiography was therefore used to confirm PM perfusion; the basic infarct territories defined by LCX branch occlusions have been reported by Llaneras et al. 

These considerations are therefore helpful when we consider this study in the perspective of the prior literature. The concept that “failure of the PM to contract may actually compensate for the altered spatial relationships... so that the valve leaflets come into better apposition” was actually advanced as an explanation for a decrescendo murmur of ischemic MR by Burch et al. 

Despite this, Kisanuki et al. 

considered PM contractile dysfunction with ischemic MR; however, this dysfunction was also accompanied by more widespread LV dysfunction in their clinical series, with the potential for more severe tethering. Our study used a model of inferobasal ischemia resembling the pattern seen in many patients with ischemic MR to test the hypothesis that ischemic MR can actually be diminished by PM contractile dysfunction. It is reasonable to suppose, however, that with more severe LV dilation and tethering, ischemic MR is likely to persist regardless of PM inactivation.

Conclusions

Papillary muscle contractile dysfunction can paradoxically decrease MR caused by ischemic distortion of the inferior base of the left ventricle; it does so by reducing leaflet tethering to promote more effective leaflet closure. Three-dimensional, contrast, and Doppler strain rate echocardiographic techniques provide physiological tools to support this conclusion, which emphasizes the importance of geometric factors in the mechanism and potential therapy of this complication of ischemic heart disease.

<table>
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<tr>
<th>Hemodynamic, LV, Mitral Valve, and PM Measurements</th>
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<tr>
<td><strong>Baseline (1)</strong></td>
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<tr>
<td>Heart rate, bpm</td>
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<td>LVP, mm Hg</td>
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<td>LAP, mm Hg</td>
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<td>LVP-LAP, mm Hg</td>
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<td>LV dp/dt, mm Hg/s</td>
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<td>LVEDV, mL</td>
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<td>LVESV, mL</td>
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<td>EF, %</td>
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<td>MR regurgitation volume, mL</td>
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<td>MR orifice area, mm²</td>
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<td>Tethering length, axial component (medial PM, mm)</td>
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<td>MA area, cm²</td>
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<td>Closing force, mm Hg/cm²</td>
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<td>PM % thickening (SAX)</td>
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<td>PM % thickening (M-mode)</td>
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<td>Strain rate, s⁻¹</td>
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LVP indicates LV pressure; LAP, LA pressure; LVED, LV end-diastolic volume; LVES, LV end-systolic volume; tethering length, distance of PM from mitral annulus (MA); and SAX, short axis. All 2-way ANOVAs but one (heart rate) were significant (P<0.01). Significant changes (P<0.01, Bonferroni) are indicated for 2-way comparisons.

*Baseline vs inferior ischemia, †inferior ischemia vs inferior + PM ischemia.
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