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

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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±2.8%). Adding PM ischemia consistently decreased MR and tethering distance (5.2±0.3 to 1.4±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

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Mitar 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 to close more effectively.

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 only not to sharpen our understanding of mechanism but also practically because abnormal tethering can potentially be addressed mechanically, 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 1; can be found Online at http://www.circulationaha.org); the guiding catheter was then withdrawn. The perfusion catheter had a side-hole entry port with its tip placed within the circumflex, just before the origin of the second obtuse marginal branch.

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 ligation. 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. Three-dimensional LV volumes were obtained through endocardial borders from 9 views. MR stroke volume was calculated as LV ejection volume minus aortic outflow volume directly measured by flowmeter. and MR orifice area was calculated from regurgitant stroke volume minus aortic outflow volume directly measured by flowmeter.22
Short-axis views showing preserved PM thickening despite inferobasal ischemia during diastole (C) and systole (D).

PM Assessment
PM perfusion was confirmed when ischemia was limited to the inferobasal wall by injecting 3 mL of agitated saline echo contrast into the 6F perfusion catheter at its carotid entry port (Figures 3A and 3B). Three complementary measures assessed PM contraction: (1) cross-sectional mid-PM thickening (Kaul et al,11 Figures 3C and 3D); (2) M-mode thickening from endocardial to PM interfaces by epicardial probe over the PM; and (3) longitudinal contraction by strain rate. The rate of change of the length between PM insertion and tip equals the difference in the velocity of these two points; dividing by initial length gives strain rate. This was measured with the low-pass filter of an ATL HDI 5000 scanner, with velocity components parallel to the PM long axis used to assess longitudinal contraction.

Statistical Analysis
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

Mitra 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 (compare Figure 1).

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. 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. 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.

Implications
Mechanistically, these results emphasize the central role of geometric changes and tethering in causing ischemic MR. Practically, they lend further support to therapeutic efforts directly targeting the fundamental tethering imbalance that restricts leaflet closure, either by plicating distorted infarct regions or by resecting myocardium between the PMs. Such interventions aim to overcome the variable, often frustrating results of annuloplasty techniques that only incompletely address tethering at the annular end. The benefit of preventing ischemic distortion can also be a factor in decisions regarding thrombolysis in acute inferior infarctions despite their often limited size. 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, 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
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.\textsuperscript{15,16} Future quantitative 3D reconstruction could potentially be facilitated by voxel and real-time 3D echocardiography.\textsuperscript{33,34} Because of the difficulties in measuring PM contraction without implanted markers that may disturb the muscles, we used several complementary techniques, including strain-rate measurement, as well as the demonstration of perfusion and the published technique of Kaul and colleagues\textsuperscript{11} of measuring cross-sectional thickening (used to confirm MR with global ischemia and maintained PM perfusion\textsuperscript{11}). Although LV-unattached PM length may be greater in some patients,\textsuperscript{35} that would in fact favor ischemic PM elongation, decreasing MR as observed.

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.
References

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