Mechanism of Ischemic Mitral Regurgitation
An Experimental Evaluation
Sanjiv Kaul, MD; William D. Spotnitz, MD;
William P. Glasheen, PhD; and Dale A. Touchstone, MD

Background. Papillary muscle dysfunction (PMD) has been implicated in the pathogenesis of ischemic mitral regurgitation (MR). We hypothesized that ischemic MR is not caused by PMD and/or dysfunction of the myocardial regions from where the papillary muscles arise but is related to reduction in global left ventricular (LV) function. To test this hypothesis, three groups of dogs were studied.

Methods and Results. In group 1 dogs \((n=8)\), varying degrees of regional and global LV dysfunction were produced. In group 2 dogs \((n=7)\), the circulation to the papillary muscles was isolated from that of the rest of the LV. Dysfunction of one or both papillary muscles was produced without producing global LV dysfunction. Global LV dysfunction was also produced while keeping papillary muscle function intact. The degree of MR (assessed using contrast echocardiography) was correlated in both groups of dogs with thickening of the papillary muscles and regional and global LV function. In the group 3 dogs \((n=6)\), the spatial distribution of blood flow within each papillary muscle was determined during ischemia by using radiolabeled microspheres. Thickening of the papillary muscles was assessed at three different levels along their lengths and was correlated with average blood flow at these levels.

In group 1 dogs, MR was noted only when global LV function was affected and its severity correlated inversely with global LV function \((r=-0.84\) with peak positive LV dP/dt and \(r=-0.95\) with global LV thickening, respectively). In comparison, there was poor correlation between MR and anterior and posterior papillary muscle thickening \((r=-0.38\) and \(r=-0.49\), respectively). In group 2 dogs, MR did not occur in the presence of either PMD or akinesia of the immediately adjacent LV myocardium. MR occurred only when global LV dysfunction was produced (with the papillary muscle function intact), and its severity correlated inversely with global LV function \((r=-0.92\) with LV dP/dt and \(r=-0.86\) with global LV thickening, respectively). There was poor correlation between the degree of MR and thickening of the anterior and posterior papillary muscles \((r=-0.24\) and \(r=-0.38\), respectively). In both groups of dogs, MR was associated with incomplete mitral leaflet closure (IMLC), and the severity of MR correlated linearly with the degree of IMLC \((r=0.98)\). MR was never associated with mitral valve prolapse. In the group 3 dogs, despite more inhomogeneous flow during ischemia to the anterior compared with the posterior papillary muscle, mean thickening of these muscles was similar \((3\pm10\%\) and \(3\pm4\%,\) respectively). Furthermore, there was minimal variability in thickening between different parts of the muscles \((3\pm2\%\) and \(5\pm3\%,\) respectively).

Conclusions. It is concluded that PMD and/or dysfunction of the immediately adjacent LV myocardium does not result in MR. MR occurs during ischemia only when global LV function is affected, even when thickening of the papillary muscles and the immediately adjacent LV remains intact. MR in this situation is related to IMLC; the greater the degree of IMLC, the greater the MR. These findings suggest that the mechanism of ischemic MR is not related to PMD. There may also be important therapeutic implications of these findings. (Circulation 1991;84:2167–2180)

There is controversy regarding the mechanism of mitral regurgitation (MR) occurring as a consequence of myocardial ischemia. A variety of mechanisms have been postulated, most of which are based on either mitral leaflet prolapse or incomplete mitral leaflet closure (IMLC) as the anatomic cause of ischemic MR. In almost all instances, the papillary muscles have been implicated in the pathogenesis of this condition.\(^1\)–\(^{10}\)

It has been proposed that as the left ventricular (LV) apex and the mitral annular plane approximate each other in systole, the occurrence of papillary
muscle shortening prevents prolapse of the mitral leaflets. Based on this assumption, Burch and colleagues\(^1\) postulated that ischemia or infarction of a papillary muscle results in its lack of shortening during systole, causing the mitral leaflets to prolapse with resultant MR. Although these authors described clinical,\(^2\) electrocardiographic,\(^3\) and M-mode echocardiographic\(^4\) features that purportedly were characteristic of papillary muscle dysfunction (PMD), they never proved that PMD occurred in the context of ischemic MR or that it caused MR.

Several investigators\(^5\)--\(^8\) have since demonstrated that damage to either papillary muscle does not result in MR in the dog. Tsakiris et al\(^7\) and Mittal and colleagues\(^8\) noted MR only when they produced damage to the papillary muscles and the adjacent LV myocardium. Based on these findings, Mittal and colleagues concluded that both PMD and regional LV dysfunction are required to produce ischemic MR. With the advent of two-dimensional echocardiography, it became possible to study the orientation of the mitral leaflets in relation to the mitral annular plane. Using this technique, Ogawa et al\(^9\) reported that, in the majority of their patients with ischemic heart disease and MR, the mitral leaflet coaptation point was caudal to the mitral annular plane in end systole. The term IMLC was coined by Godley and coworkers\(^10\) to describe this finding. The occurrence of IMLC, however, was attributed by these authors to dyskinesia in the region of the LV from where the papillary muscles arise. It was postulated that regional dyskinesia results in outward pulling of the papillary muscle in systole, preventing the mitral leaflets from returning to the mitral annular plane.

We and others\(^11\)--\(^13\) have since reported that IMLC is seen even in the absence of regional dyskinesia and is associated with almost any condition where significant global LV dysfunction is seen (with or without associated regional LV dysfunction). Using Doppler echocardiography, we have also confirmed that IMLC is invariably associated with MR.\(^12\) In the present study, we therefore hypothesized that ischemic MR is not caused by PMD or dysfunction of the regions of the LV from where these muscles arise but is related to the occurrence of global LV dysfunction. We tested this hypothesis by means of two-dimensional echocardiography in unique models of regional and global ischemic LV dysfunction and isolated ischemic PMD.

### Methods

Twenty-one dogs were included in the study. Group 1 consisted of eight dogs in which regional and global LV dysfunction of various degrees were produced. Group 2 comprised seven dogs in which the circulation to the papillary muscles was isolated from that of the rest of the LV. Dysfunction of one or both papillary muscles was produced without producing global LV dysfunction. Global LV dysfunction was also produced while keeping papillary muscle function intact. The degree of MR was correlated in both groups of dogs with thickening of the papillary muscles, degree of IMLC, and regional and global LV function. Group 3 included six dogs in which the spatial distribution of blood flow within each papillary muscle was determined during ischemia by using radiolabeled microspheres. Thickening of each papillary muscle was assessed at three different levels along its length and correlated with blood flow at these levels.

The dogs were anesthetized with 30 mg/kg intravenous sodium pentobarbital, intubated, and ventilated using a dual-phase control respirator pump (model 607, Harvard Apparatus, South Natick, Mass.). An 8F catheter was placed in the left femoral artery for monitoring arterial pressure and arterial blood gases. This catheter was connected to a physiological recorder (model 4568C, Hewlett-Packard Co., Waltham, Mass.) via a fluid-filled pressure transducer (model 1280C, Hewlett-Packard Co.). This catheter was also used for the withdrawal of reference blood samples during left atrial (LA) injection of radiolabeled microspheres in group 3 dogs. A similar catheter was placed in the left femoral vein for the administration of fluids and drugs as needed. Blood gases were monitored every hour, \(\text{FiO}_2\) and respiratory rate were adjusted, and intravenous sodium bicarbonate was administered as needed.

A median sternotomy or a left lateral thoracotomy was performed, and the heart was suspended in a pericardial cradle. A bolus of 2 mg/kg lidocaine was administered intravenously followed by an infusion at a rate of 2 mg/min. A micromanometer-tipped catheter (Millar Instruments, Houston, Tex.) was inserted into the LV cavity via a small incision in the LV apex and secured in place using a purse-string suture. This catheter was connected to the physiological recorder and was used to measure LV pressures, including peak positive LV \(\text{dP/dt}\), and for the injection of contrast into the LV cavity. A 22-gauge catheter placed in the LA and connected to the physiological recorder was also used to inject radiolabeled microspheres in the group 3 dogs.

In group 2 and 3 dogs, two-dimensional echocardiography was performed to identify the coronary arterial branches supplying each of the papillary muscles. The transducer was moved manually over...
The surface of the heart until the papillary muscle in question was seen directly below the transducer. The major artery immediately in the proximity of the transducer was determined to be the vessel supplying that papillary muscle. These usually corresponded to a major diagonal branch of the left anterior descending coronary artery (LAD) for the anterior papillary muscle and an obtuse marginal branch of the left circumflex coronary artery (LCx) for the posterior papillary muscle. The proximal portions of these vessels were dissected free from the surrounding tissues and snare were placed loosely around them.

**Group 1 Dogs**

The left main artery (LM) and the proximal portions of the LAD and LCx arteries were dissected free from surrounding tissues and snares were placed loosely around them (see Figure 1). An appropriately sized electromagnetic flow probe (model EP406, Carolina Medical Electronics, King, N.C.) was placed around the LCx just proximal to the snare and connected to a flowmeter (model FM502, Carolina Medical Electronics). A 22-gauge intravascular catheter was placed in a branch of the LAD and connected to the physiological recorder via a pressure transducer.

The right femoral artery was exposed, and a 12F cannula was inserted. This cannula was attached to plastic tubing placed in a constant-flow roller pump (Varistaltic Series S, Manostat, New York, N.Y.). The other end of this tubing was connected to a Gregg cannula. The entire system was primed with heparinized saline, and the Gregg cannula was inserted into the ascending aorta via an incision in the left innominate artery. Ten thousand international units of heparin was injected intravenously, and the roller pump was started at a slow speed to replace the saline in the system with blood. The tip of the Gregg cannula was introduced into the LM lumen and secured there with the preplaced snare. The roller pump was adjusted so that the LCx flow and the distal LAD pressure were similar before and after the introduction of the cannula.

**Group 2 Dogs**

Both internal mammary arteries were dissected from their origins to the level of the xiphoid process (see Figure 2). Ligatures were placed on the side branches of these vessels to achieve hemostasis. After administration of 20,000 IU of heparin, the dissected portions of the arteries were transected for use as bypass grafts. Plastic cannulae were placed in the proximal ends of the grafts and secured there with ties. Each cannula was connected to plastic tubing.

The right femoral artery was cannulated with a 14F catheter. Venous cannulae (28F) were placed in the superior vena cava and the right ventricle via the right atrium. The dogs were placed on cardiopulmonary bypass by using a roller pump (model 6002, Sarns, Ann Arbor, Mich.) and a bubble oxygenator (S-100A, Shiley, Irvine, Calif.). They were cooled to a blood temperature of 30°C by using a heat pump (Blanketrol 200 HL, Sub-Zero Products, Cincinnati, Ohio). A cannula was placed in the aortic root for delivery of cardioplegic solution. The aorta was cross-clamped proximal to the origin of the right brachiocephalic artery and cardiac arrest was established by delivering 150 ml of ice-cold cardioplegic solution to the aorta.

Anastamoses were performed between the non-cannulated ends of the internal mammary artery grafts and the vessels previously identified on two-dimensional echocardiography as supplying the two papillary muscles. Anastamotic patency was con-
firmed with a 1.5-mm probe. The aortic cross-clamp was removed, and the dogs were rewarmed to a blood temperature of 35°C. They were weaned from cardiopulmonary bypass with the aid of an intravenous infusion of 10 μg/kg/min dobutamine.

Blood from the left carotid artery was used to perfuse the papillary muscles and the immediately adjacent LV myocardium. The left carotid artery was exposed, and a 12F cannula was placed in it. This cannula was connected to plastic tubing that was placed in a roller pump (Varisaltic Series S, Manostat). The other end of this tubing was attached to the base of a Y connector. The two distal ends of the Y connector were attached via stopcocks to the plastic tubing previously attached to the internal mammary artery grafts supplying the papillary muscles. These stopcocks were also connected to the physiological recorder via pressure transducers.

Blood was withdrawn from the aortic root and used to perfuse the rest of the LV myocardium via the LM artery; to do this, the LM artery was first dissected free from surrounding tissues and a tie was placed loosely around it. The catheter, previously placed in the aortic root for cardioplegia delivery, was now connected to plastic tubing, the other end of which was attached to a Gregg cannula. The tubing was placed in a roller pump, the system was primed with arterial blood, and the Gregg cannula was introduced into the ascending aorta via an incision in the left brachiocephalic artery. The tip of the Gregg cannula was maneuvered into the LM and secured there with the preplaced tie.

Two-dimensional Echocardiography

Two-dimensional echocardiography was performed using 5-MHz transducers (Mark-III, Advanced Technology Laboratories, Bellevue, Wash., for group 1 dogs; ND-256, Biosound, Indianapolis, Ind. for group 2 dogs; and RT-5000, General Electric, Milwaukee, Wis. for group 3 dogs). A saline-filled bath acted as an acoustic interface between the heart and the transducer. Images were recorded on videotape with a 1.27-cm VHS recorder (Panasonic model NV-8950, Matsushita Electric, Japan).

To assess the severity of MR in the group 1 and 2 dogs, contrast was injected into the LV cavity through the micromanometer-tipped catheter placed in the LV apex (Figure 3A). The contrast agent consisted of 4 ml of hand-agitated mixture of Renografin-76 (Squibb, New Brunswick, N.J.) and 0.9% saline. Images were acquired in the apical four-chamber (group 1) or parasternal long-axis (group 2) views. To delineate the perfusion of each papillary muscle in group 2 dogs, 0.5 ml of 1:5 dilution of Albunex® (Molecular Biosystems, San Diego, Calif.) was used. This agent was injected into both the grafts connected to the vessels supplying the papillary muscles to ensure that the grafts were patent and were in fact perfusing the papillary muscles.

**Figure 3.** Schematic drawings show echocardiographic methods for assessing degree of mitral regurgitation, degree of incomplete mitral leaflet closure, and left atrial size in group 1 dogs (panel A); left ventricular end-diastolic and end-systolic areas at three short-axis levels in group 1 dogs (panel B); and left ventricular wall thickening and papillary muscle thickening in group 1 and 2 dogs (panel C).

**Analysis of Echocardiographic Images**

An off-line image analysis system (Mipron, Kontron Electronics, Eching, FRG) was used for analysis of the two-dimensional echocardiography images. In group 1 dogs, the short-axis area of the LV chamber was measured both in end diastole and end systole at the mitral valve, midpapillary muscle, and apical levels (Figure 3B). These areas were added, and the change in total area from end diastole to end systole was calculated. In group 2 dogs, changes in LV short-axis area were calculated only at the midpapillary muscle short-axis level. In group 1 and 2 dogs, LV wall thickening was measured at the midpapillary muscle short-axis level. The endocardial and epicardial contours were outlined both in end diastole and end systole. The computer automatically calculated wall thickness in 32 chords along the LV circumference (Figure 3C). The average thickening along the 32 chords represented global LV thickening. Average thickening within the operator defined regions of reduced thickening during ischemia were also automatically calculated.

Thickening of the papillary muscles in group 1 and 2 dogs was also measured at the midpapillary muscle short-axis level (Figure 3C). It was measured as a change in papillary muscle area from end diastole to end systole. If a papillary muscle had more than one
head, the areas for all the heads were added to represent papillary muscle size. Thickenings was represented by averaging data from three consecutive cycles. In group 3 dogs, in addition to the midpapillary muscle level, papillary muscle thickening was also measured at the upper and lower papillary muscle short-axis levels. In addition, long-axis views of the papillary muscles were also obtained in this group of dogs and thickening along the transverse dimension of these muscles was measured at three different levels along the length of each muscle. In two group 1 dogs, the two-dimensional echocardiography quality prevented quantitation of papillary muscle thickening.

In group 2 dogs, the area of each papillary muscle showing contrast (after injection of contrast into the graft supplying that muscle) was expressed as a percent of the total papillary muscle area. This measurement was performed to determine the extent to which a papillary muscle received dual blood supply. During this injection, the region of the LV adjacent to each papillary muscle was also defined. This region was marked on a plastic overlay for the assessment of wall thickening within this region. Figure 4 depicts images from one of the group 2 dogs after contrast was injected into the grafts supplying the papillary muscles.

Mitril annular dimension and the distance between the mitral leaflet coaptation point and the mitral annular plane (which represents the degree of IMLC) were measured at end systole in the apical four-chamber view in the group 1 dogs (Figure 3A). LA size was derived by multiplying the longitudinal and transverse LA dimensions. When contrast was injected into the LV, if there was no appearance of contrast in the LA, MR was assessed as 0. If only a small amount of contrast appeared in the LA and disappeared in fewer than three beats, it was assessed as 1/2+. Equal opacification of the LV and LA with contrast taking equally long to disappear from both chambers was assessed as 4+ MR. The intermediate stages were assessed as 1+ to 3+, based on the amount of contrast appearing in the LA and the rate of its clearance from the LA. Half grades were also used.

Measurement of Blood Flow to the Papillary Muscles

Blood flow to the papillary muscles in group 3 dogs was determined by injecting 2×10⁶ radiolabeled microspheres (DuPont Medical, Wilmington, Del.) into the LA just after the initiation of withdrawal of arterial blood from the left femoral artery. Ten milliliters of arterial blood was withdrawn over 90 seconds using a constant rate pump (model 644, Harvard Apparatus). The 11-μm microspheres were agitated in 4 ml of solution of 0.9% saline and 0.01% Tween-80 before injection. At the end of the experiment, the animals were killed. The heart was excised and the LV was cut into three slices corresponding to the short-axis slices at the lower, mid, and upper papillary muscle two-dimensional echocardiography levels. The section of the papillary muscle cut at each level was removed and sliced further into medial, central, and lateral segments. In this manner, each papillary muscle was cut into nine segments. These segments and the reference samples were counted for 500 seconds in a well counter with a multichannel analyzer (Auto-Gamma Scintillation Spectrometer model 5986, Packard, Downer’s Grove, Ill.). Blood flow to each segment was calculated using previously described methods.

Hemodynamic Measurements

Heart rate and arterial and LV pressures as well as peak positive LV dP/dt were measured in all group 1 dogs. Peak positive LV dP/dt could not be measured in two of the group 2 dogs because of technical reasons. LA pressure was measured only in group 1 dogs. Hemodynamic and two-dimensional echocar-
diographic recordings were initiated and terminated simultaneously during each stage. Hemodynamic measurements represented an average of 10 consecutive beats in the middle of the recording.

Protocol

In group 1 dogs, the LAD and LCx were occluded in random order and the presence of occlusion was confirmed by either lack of flow (LC) or severe reduction in distal arterial pressure (LAD) and by regional LV dysfunction on two-dimensional echocardiography. Each occlusion lasted for about 5 minutes. Global ischemia was produced by reducing flow to the LM artery to moderately and severely low levels. Five to 10 minutes were allowed between stages for hemodynamic equilibration. If ventricular tachycardia or fibrillation occurred at any stage, the occlusion was immediately reversed and the dog was defibrillated. If the dog survived, the experiment was continued. If a dog did not survive stages representing both regional and global LV dysfunction, it was not included in the study.

In group 2 dogs, flow to the papillary muscles was abolished in random order by occluding the graft as well as the native vessel supplying each muscle. The lack of flow was confirmed by the pressure in the graft. When global hypokinesis was caused by reducing flow to the LM artery, flow to the grafts was adjusted so the pressure in the grafts remained similar to that at baseline. In all dogs, one or more of the stages were repeated. Each stage lasted approximately 5 minutes, and 5–10 minutes were allowed between stages for hemodynamic equilibration.

In group 3 dogs, the vessel supplying the anterior papillary muscle was first occluded. Five minutes later, papillary muscle blood flow and two-dimensional echocardiographic data were acquired. The occlusion was reversed, and the vessel supplying the posterior papillary muscle was then occluded. Blood flow and two-dimensional echocardiographic data were acquired 5 minutes later. At the end of the experiment, all the dogs were killed.

Statistical Analysis

Data are expressed as mean±1 SD. Correlation between the degree of MR (0 to 4+) and different hemodynamic and two-dimensional echocardiographic parameters in each dog was performed using Spearman’s rank correlation.19 The variability in the blood flow and thickening of the papillary muscles was expressed as the square root of the total variance. Differences in the hemodynamic data between stages was evaluated using analysis of variance with repeat measures.19

Results

Group 1 Dogs

Table 1 lists the baseline two-dimensional echocardiography measurements in group 1 dogs. Trace MR was noted in four dogs even at baseline. In two, there

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**Table 1. Baseline Echocardiographic Measurements in Group 1 Dogs**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left atrial size</td>
<td>6.3±0.7 cm²</td>
</tr>
<tr>
<td>Mitral annular dimension</td>
<td>2.7±0.3 cm</td>
</tr>
<tr>
<td>Systolic change in LV thickening (midpapillary muscle level only)</td>
<td>34±11%</td>
</tr>
<tr>
<td>Systolic change in LV area</td>
<td>25±6%</td>
</tr>
<tr>
<td>Distance between mitral leaflet coaptation point and mitral annular plane in end systole</td>
<td>0.25±0.07 cm</td>
</tr>
<tr>
<td>Degree of mitral regurgitation</td>
<td>0.30±0.42</td>
</tr>
<tr>
<td>APM end-diastolic area</td>
<td>0.98±0.23 cm²</td>
</tr>
<tr>
<td>Systolic change in APM area</td>
<td>36±17%</td>
</tr>
<tr>
<td>PPM end-diastolic area</td>
<td>0.86±0.22 cm²</td>
</tr>
<tr>
<td>Systolic change in PPM area</td>
<td>33±20%</td>
</tr>
</tbody>
</table>

LV, left ventricular; APM, anterior papillary muscle; PPM, posterior papillary muscle.

Values are mean±1 SD. n=8 dogs.

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was mild mitral valve prolapse. Figures 5 and 6 illustrate two-dimensional echocardiographic data from one of our group 1 dogs. At baseline, this dog

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**Figure 5.** Images and illustrations show modified four-chamber view during left circumflex artery occlusion. Mild incomplete mitral leaflet closure (panel A) and mild mitral regurgitation (panel B) are seen despite complete lack of thickening of the entire inferoposterior wall and the posterior papillary muscle. There was mild reduction in global left ventricular function. LV, left ventricle; RV, right ventricle; IMLC, incomplete mitral leaflet closure; LA, left atrium; Ao, aorta.
FIGURE 6. Images and illustrations show modified four-chamber view during global hypokinesia of the left ventricle (LV). Marked degree of incomplete mitral leaflet closure (IMLC) (panel A) and severe mitral regurgitation is noted (panel B). RV, right ventricle; LA, left atrium; RA, right atrium.

demonstrated no mitral valve prolapse, IMLC, or MR. During LC occlusion, there was total lack of thickening of the posterior papillary muscle and a large area of inferoposterior LV wall. Compensatory hyperkinesia of the anterior wall so that global LV function was only mildly reduced was seen. Only mild MR was noted and was associated with mild IMLC (Figure 5). In contrast, when flow to the entire LV myocardium was reduced, causing global hypokinesis, the degree of IMLC was greatly enhanced and severe MR was produced (Figure 6).

Table 2 lists the hemodynamic data in this group of dogs at baseline and during different stages of ischemia. There is resting tachycardia during pentobarbital anesthesia. During occlusion of either the proximal LAD or the proximal LC, there is mild reduction in mean aortic pressure with a significant rise in the LA and LV end-diastolic pressures. Peak positive LV dp/dt is reduced more during LCx compared with LAD ischemia. During moderate global ischemia, the hemodynamic data show further worsening of LV function, whereas during severe global LV ischemia, there is a very significant decrease ($p<0.01$) in the mean aortic pressure with a further decrease in peak positive LV dp/dt. LA and LV end-diastolic pressures, however, were not affected to a similar degree.

Figure 7 illustrates the relation between the severity of MR and various hemodynamic and two-dimensional echocardiographic parameters in the dog whose data are illustrated in Figures 5 and 6. Nine separate stages were recorded in this dog. Various degrees of global LV dysfunction were produced. There was a close inverse relation between peak positive LV dp/dt and the severity of MR (Figure 7A) and also between the percent systolic global LV thickening and the severity of MR (Figure 7B). The degree of IMLC had a close linear relation with the severity of MR (Figure 7C). In contrast, the percent thickening of the anterior (filled circles) and posterior (open circles) papillary muscles correlated poorly with the severity of MR (Figure 7D).

Table 3 shows the average correlation between the severity of MR and two-dimensional echocardiographic and hemodynamic parameters in all eight dogs. All parameters that reflect global LV systolic function (peak positive LV dp/dt, mean aortic pressure, global wall thickening, and percent change in LV area from end diastole to end systole) generally correlate closely and inversely with the severity of MR. A close linear relation between the severity of MR and LV end-diastolic size and end-systolic LA and mitral annular dimensions was also noted in this group of dogs.

Group 2 Dogs

Table 4 depicts the baseline two-dimensional echocardiographic measurements in group 2 dogs. Ninety-

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**TABLE 2. Hemodynamic Data in Group 1 Dogs**

<table>
<thead>
<tr>
<th>Hemodynamic variable</th>
<th>Baseline</th>
<th>LAD ischemia</th>
<th>LCx ischemia</th>
<th>Moderate global ischemia</th>
<th>Severe global ischemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>130±21</td>
<td>119±21</td>
<td>132±18</td>
<td>121±19</td>
<td>120±38</td>
</tr>
<tr>
<td>Mean AoP (mm Hg)</td>
<td>79±24</td>
<td>66±24</td>
<td>67±26</td>
<td>60±14</td>
<td>30±8*</td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
<td>4±5*</td>
<td>15±17</td>
<td>14±8</td>
<td>13±9</td>
<td>15±9</td>
</tr>
<tr>
<td>Peak positive LV dp/dt</td>
<td>1,816±281†</td>
<td>1,471±694</td>
<td>1,157±573</td>
<td>1,120±409</td>
<td>9,07±526</td>
</tr>
<tr>
<td>Mean LAP (mm Hg)</td>
<td>3±4*</td>
<td>11±12</td>
<td>15±12</td>
<td>15±7</td>
<td>17±17</td>
</tr>
</tbody>
</table>

LAD, left anterior descending artery; LCx, left circumflex artery; AoP, aortic pressure; LVEDP, left ventricular end-diastolic pressure; LV, left ventricular; LAP, left atrial pressure.

Moderate global ischemia achieved in five dogs; severe global ischemia achieved in seven dogs; n=8 dogs.

* $p<0.01$ by analysis of variance.

† $p<0.05$ by analysis of variance.
two percent of the anterior and 85% of the posterior papillary muscle in all seven dogs was supplied by the bypass grafts. Only one dog had MR at baseline, which was mild. Figure 8 illustrates normal contraction of both the LV walls and the papillary muscles from end diastole (panel A) to end systole (panel B) in one of the group 2 dogs at baseline. Trace MR was noted in this stage. In comparison, when global LV dysfunction was produced, despite adequate thickening of the papillary muscles and the immediately adjacent LV walls (Figure 7C and 7D), the degree of IMLC increased and severe MR was produced. Reversal of regional and global LV dysfunction resulted in normalization of the two-dimensional echocardiographic and hemodynamic parameters and disappearance of MR in every case.

Table 5 lists the hemodynamic data in this group of dogs at baseline and during ischemia of either one or both papillary muscles and during global LV ischemia. The resting tachycardia probably reflects both pentobarbital anesthesia and the postcardiopulmonary bypass state. Ischemia of either one or both papillary muscles does not result in a major change in mean aortic and LV end-diastolic pressures, whereas

<table>
<thead>
<tr>
<th>Hemodynamic data</th>
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<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>-0.24</td>
</tr>
<tr>
<td>Mean aortic pressure (mm Hg)</td>
<td>-0.87</td>
</tr>
<tr>
<td>LV end-diastolic pressure (mm Hg)</td>
<td>0.45</td>
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<tr>
<td>Peak positive LV dP/dt</td>
<td>-0.83</td>
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<tr>
<td>Left atrial pressure (mm Hg)</td>
<td>0.67</td>
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<table>
<thead>
<tr>
<th>Echocardiographic data</th>
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</thead>
<tbody>
<tr>
<td>Left atrial size (cm²)</td>
<td>0.74</td>
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<tr>
<td>Mitral annular size (cm)</td>
<td>0.91</td>
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<tr>
<td>LV end-diastolic area (cm²)</td>
<td>0.78</td>
</tr>
<tr>
<td>Δ LV area</td>
<td>-0.86</td>
</tr>
<tr>
<td>Average LV wall thickening</td>
<td>-0.95</td>
</tr>
<tr>
<td>APM thickening*</td>
<td>-0.38</td>
</tr>
<tr>
<td>PPM thickening*</td>
<td>-0.49</td>
</tr>
<tr>
<td>Distance between mitral leaflet coaptation point and mitral annular plane (cm)</td>
<td>0.98</td>
</tr>
</tbody>
</table>

n=8 dogs; 42 observations.

*Obtained in six dogs (34 observations).

LV, left ventricular; APM, anterior papillary muscle; PPM, posterior papillary muscle.
TABLE 4. Baseline Echocardiographic Measurements in Group 2 Dogs

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic change in LV area (papillary muscle level only)</td>
<td>43±7%</td>
</tr>
<tr>
<td>Systolic change in LV thickening (papillary muscle level only)</td>
<td>38±5%</td>
</tr>
<tr>
<td>Systolic change in thickening of region of the LV adjacent to APM</td>
<td>42±7%</td>
</tr>
<tr>
<td>Systolic change in thickening of region of the LV adjacent to PPM</td>
<td>38±7%</td>
</tr>
<tr>
<td>Distance between mitral leaflet coaptation point and mitral annular plane in end systole (cm)</td>
<td>0.38±0.06</td>
</tr>
<tr>
<td>Degree of mitral regurgitation</td>
<td>0.04±0.09</td>
</tr>
<tr>
<td>APM end-diastolic area (cm²)</td>
<td>1.09±0.25</td>
</tr>
<tr>
<td>Systolic change in APM area</td>
<td>39±15%</td>
</tr>
<tr>
<td>PPM end-diastolic area (cm²)</td>
<td>1.06±0.14</td>
</tr>
<tr>
<td>Systolic change in PPM area</td>
<td>37±10%</td>
</tr>
<tr>
<td>APM perfused by bypass graft</td>
<td>92±14%</td>
</tr>
<tr>
<td>PPM perfused by bypass graft</td>
<td>85±20%</td>
</tr>
</tbody>
</table>

n=7 dogs. LV, left ventricular; APM, anterior papillary muscle; PPM, posterior papillary muscle.

A significant decrease in peak positive LV dP/dt is noted. When global LV ischemia is produced (with both papillary muscles and the adjacent LV walls showing normal contraction), profound global LV dysfunction is noted. There is a very significant decrease (p<0.01) in the mean aortic pressure as well as in the peak positive LV dP/dt and a major increase (p<0.01) in the LV end-diastolic pressure.

Figure 9 illustrates the relation between various hemodynamic and two-dimensional echocardiographic parameters and the severity of MR in the dog whose data are depicted in Figure 8. Seven stages were recorded in this dog. There were excellent inverse correlations between parameters of global LV systolic function such as peak positive LV dP/dt (Figure 9A) and average LV wall thickening (Figure 9B). There was a close linear correlation between the degree of IMLC and the severity of MR (Figure 9C). The relation between anterior (filled circles) and posterior (open circles) papillary muscle thickening and the severity of MR was poor (Figure 9D).

Table 6 lists the average correlations between the severity of MR and two-dimensional echocardiographic and hemodynamic parameters in group 2 dogs. The parameters of LV systolic function such as peak positive LV dP/dt, aortic pressure, global LV thickening, and the percent change in LV dimension from end diastole to end systole demonstrated a close inverse relation with the severity of MR. Thickening of the papillary muscles and the region of the myocardium adjacent to the muscles did not correlate with the severity of MR. The degree of IMLC correlated closely with the severity of MR.

In no dog in either group 1 or 2 was mitral valve prolapse associated with regional or global LV dysfunction. In each case (including the two group 1 dogs with mild prolapse at baseline), IMLC was noted when significant global LV dysfunction was produced. The degree of IMLC had a direct and close relation with the severity of MR in all dogs. The greater the degree of IMLC, the greater the severity of MR. Reversal of global and regional ischemia resulted in normalization of all two-dimensional echocardiographic and hemodynamic parameters including mitral leaflet coaptation and disappearance of any MR.

**Group 3 Dogs**

Despite occluding the major vessel supplying the anterior papillary muscle, blood flow to the lateral segments of this muscle was normal at all three short-axis levels in all six dogs. The mean flow to this normally perfused region was 0.95±0.31 ml/min/g. In comparison, the flows to the central and medial parts of this muscle were markedly reduced, with the mean flow to these regions being 0.10±0.07 ml/min/g. The variability of flow within these six ischemic segments was modest (0.08±0.08 ml/min/g). Despite adequate flow to parts of the anterior papillary muscle, its thickening was severely reduced. The mean change in short-axis area was 3±10% during ischemia compared with 38±16% at baseline (p<0.01). The mean variability in thickening at different parts of the muscle using both short- and long-axis views (upper, middle, and lower) was 3±2%.

In contrast to the anterior papillary muscle, flow to the posterior papillary muscle was homogeneously reduced in all the nine segments during occlusion of the obtuse marginal branch. The mean flow to this muscle was 0.12±0.08 ml/min/g in five of the six dogs. One dog died before we could produce ischemia of the posterior papillary muscle. The variability of flow within the entire muscle was also modest (0.12±0.09 ml/min/g). Thickening of the posterior papillary muscle was reduced during ischemia to the same extent as that of the anterior papillary muscle (3±4% in comparison with 40±9% at baseline). The mean variability in thickening at different parts of the muscle (upper, middle, and lower) using both short- and long-axis views was 5±3% during ischemia. Mitral valve prolapse was not seen during ischemia of either papillary muscle.

**Discussion**

The new information contained in this study is that localized ischemia and dysfunction of either one or both papillary muscles and/or the immediately adjacent LV myocardium does not result in MR. MR occurs only when global LV function is affected even in the presence of adequate thickening of the papillary muscles and the immediately adjacent LV myocardium. MR in this situation is invariably related to IMLC; the greater the degree of IMLC, the greater
the severity of MR. Prolapse of the mitral leaflets is not seen either during papillary muscle ischemia or during ischemia of the entire LV. These findings suggest that the mechanism of ischemic MR is independent of papillary muscle function.

**Comparison With Previous Studies**

Godley et al.\(^5\) noted IMLC in all their patients with prior infarction and MR. Similar results were reported by Gillam and colleagues\(^6\) using an experimental model of ischemia. Unlike us, however, these authors attributed their findings to regional dyskinesia, which they postulated causes outward pulling of the papillary muscles during systole. They did not correlate global LV systolic function with the degree of MR. MR was not associated with the presence or absence of dyskinesia in our dogs and was not related to the degree of wall thickening in the region from where the papillary muscles arise. In our study, MR was related only to the extent and severity of reduction in global LV function.

Similar to previous investigators,\(^5\)–\(^8\) we demonstrated that PMD does not result in MR. We extended these observations to demonstrate that MR does not occur even when the region of the LV immediately adjacent to the papillary muscles becomes dysfunctional unless this dysfunction also results in reduction in overall global LV function. Reduction in global LV function can occur if regional dysfunction involves a large portion of the myocardium. It is likely, therefore, that Tsakiris and colleagues\(^7\) and Mittal and coworkers\(^8\) produced MR in their experiments while damaging both the papillary muscles and the adjacent LV walls by also producing significant global LV dysfunction. That ischemic MR results from a combination of papillary muscle and

**Table 5. Hemodynamic Data in Group 2 Dogs**

<table>
<thead>
<tr>
<th>Hemodynamic variable</th>
<th>Baseline</th>
<th>APM ischemia</th>
<th>PPM ischemia</th>
<th>Both PM ischemia</th>
<th>Global LV ischemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>150±15</td>
<td>145±13</td>
<td>146±11</td>
<td>148±15</td>
<td>134±16</td>
</tr>
<tr>
<td>Mean AoP (mm Hg)</td>
<td>77±11</td>
<td>73±12</td>
<td>68±12</td>
<td>63±11</td>
<td>39±14*</td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
<td>6±3</td>
<td>7±3</td>
<td>8±4</td>
<td>8±4</td>
<td>14±6*</td>
</tr>
<tr>
<td>Peak positive LV dP/dt</td>
<td>2,212±301*</td>
<td>1,888±405</td>
<td>1,755±837</td>
<td>1,587±763</td>
<td>382±259*</td>
</tr>
</tbody>
</table>

\(*p<0.01\) by analysis of variance.

\(n=7\) dogs.

APM, anterior papillary muscle; PPM, posterior papillary muscle; PM, papillary muscle; AoP, aortic pressure; LVEDP, left ventricular end-diastolic pressure; LV, left ventricular.

**Figure 8.** End-diastolic (panel A) and end-systolic (panel B) short-axis images at midpapillary muscle level in one of the group 2 dogs at baseline showing adequate thickening of the left ventricular (LV) free wall and the anterior and posterior papillary muscles. End-diastolic (panel C) and end-systolic (panel D) short-axis images of the left ventricle in the same dog during decreased flow to the left main coronary artery. Global LV dysfunction is noted (dilatation of the LV cavity and poor thickening of the LV free wall). At the same time, both papillary muscles and the immediately adjacent LV myocardium demonstrate adequate thickening as flow to these regions is kept intact.
regional LV dysfunction, as suggested by Mittal and colleagues, was not confirmed in our study. MR was produced in our study only during global LV dysfunction and occurred despite adequate thickening of the papillary muscles. Our results are in concordance with our own clinical observations\(^1\) and those of others\(^{11,21,22}\) who noted ischemic MR to occur in the context of global LV dysfunction. In these studies, no differences were observed in the prevalence of MR in relation to the location of infarction or the distribution of coronary disease.

In the 14 patients with coronary artery disease and MR described by Ogawa et al,\(^9\) three were reported to have mitral valve prolapse (as opposed to nine with IMLC and two with both prolapse and IMLC).\(^9\) It is possible that these patients had prolapse even before their infarction. We agree with Godley et al,\(^10\) who, like us, were unable to demonstrate mitral valve prolapse in any of their 22 patients with prior infarction and MR that prolapse in the setting of coronary artery disease may occur fortuitously because both conditions are common. In contrast, Tei et al\(^23\) noted mitral valve prolapse when they produced transient

![Figure 9](http://circ.ahajournals.org/)

**Figure 9.** Scatterplots show relation between the severity of mitral regurgitation and several hemodynamic and echocardiographic parameters in the dog from Figure 8. There is a close inverse relation between severity of mitral regurgitation and peak positive left ventricular dp/dt (panel A) as well as left ventricular wall thickening (panel B). There is also a close linear relation between severity of mitral regurgitation and degree of incomplete mitral leaflet closure (panel C). Severity of mitral regurgitation does not correlate with thickening of either the anterior (APM) or posterior (PPM) papillary muscle (panel D).

| Table 6. Average Correlation With Degree of Mitral Regurgitation in Group 2 Dogs |
|---------------------------------|---------|
| **Hemodynamic data**            |         |
| Heart rate (beats/min)          | -0.29   |
| Mean aortic pressure (mm Hg)    | -0.81   |
| LV end-diastolic pressure (mm Hg)| 0.80    |
| Peak positive LV dp/dt\(^*\)     | -0.92   |
| **Echocardiographic data**      |         |
| LV end-diastolic area (cm\(^2\))| 0.72    |
| \(\Delta\) LV area              | -0.80   |
| Average LV wall thickening       | -0.86%  |
| Anterior wall thickening         | -0.54%  |
| Posterior wall thickening        | -0.43%  |
| APM thickening                   | -0.24%  |
| PPM thickening                   | -0.38%  |
| Distance between mitral leaflet coaptation point and mitral annular plane in end systole (cm) | 0.96 |

\(n=7\) dogs; 50 observations.

\(^*\) Obtained in five dogs (34 observations). LV, left ventricular; APM, anterior papillary muscle; PPM, posterior papillary muscle.
coronary artery occlusion in the dog. It is possible that their dogs had a higher prevalence of mitral valve prolapse at baseline. (Prolapse can also be produced artifactually by transducer malorientation.)

**Role of Papillary Muscles in Mitral Valve Mechanics**

The concept that shortening of both papillary muscles is required to prevent mitral leaflet prolapse in LV systole is not supported by our data. Mitral valve prolapse was not seen in any of our dogs in the presence of PMD, and it would appear that, in the context of mitral valve mechanics, the papillary muscles act as mere anchors preventing prolapse of the mitral leaflets during systole. If, however, the anchor is lost, as occurs during rupture of one or more papillary muscle heads (a relatively uncommon complication of acute myocardial infarction), the mitral leaflets become frail and severe MR results. MR in this condition is acute and is usually associated with a hyperdynamic LV and does not represent the more ubiquitous MR associated with ischemic LV dysfunction.

**Flow Versus Thickening of Papillary Muscles**

One concern was that in the group 1 and 2 dogs we had only measured papillary muscle thickening at the short-axis level. Furthermore, the spatial distribution of flow to each papillary muscle during ischemia was not known. To address these questions, we measured flow and thickening during ischemia of each papillary muscle in a separate group of dogs (group 3). We were also able to image the papillary muscles in greater detail, which included multiple short-axis views and the long-axis view.

We found that, unlike the posterior papillary muscle that demonstrated homogeneously reduced flow during occlusion of the obtuse marginal branch, the anterior papillary muscle could not be made homogeneously ischemic by occluding the left anterior descending artery or its diagonal branch, which is obviously related to the dual blood supply to this muscle. Despite normal flow to a part of the anterior papillary muscle, the majority of the muscle (six of the nine segments analyzed) becomes severely ischemic during LAD or diagonal artery occlusion. This degree of ischemia causes reduction in thickening equal in magnitude to that of the more homogeneously ischemic posterior papillary muscle. Furthermore, the severity of ischemia and the reduction in thickening are similar along the entire length of the papillary muscles. Whereas the dual blood supply to the anterior papillary muscle does not prevent its loss of thickening during ischemia, it might prevent necrosis of the muscle. This could be the reason why the posterior papillary muscle is far more liable to undergo partial or complete transection of one of its heads or the main body during acute myocardial infarction compared with the anterior papillary muscle.

**Mechanism of IMLC**

There are two possible mechanisms whereby IMLC can occur. It has been generally presumed that LV-LA pressure crossover results in mitral valve closure. Tsakiris and coworkers have, however, demonstrated that mitral valve closure occurs approximately 40 msec after LV-LA pressure crossover. When the afterload is increased, the leaflets close even later, whereas the opposite occurs when the afterload is reduced. From these data, it would appear that mitral valve closure may not be affected by LV-LA pressure gradient but by the rate of rise of LV pressure. It is likely that force is imparted in early systole to the almost-approximated mitral leaflets to close them completely. One of the mechanisms of IMLC, therefore, may be related to the slow rate of rise of pressure (as measured in our experiment using peak positive LV dp/dt) causing less force to be transmitted to the mitral leaflets.

The other mechanism whereby IMLC can occur may be related to poor approximation of the LV walls during systole. The close inverse relation between the change in LV area from end diastole to end systole and the severity of MR noted in our study would lend support for this mechanism. The poor approximation of the LV walls may cause incomplete approximation of the mitral leaflets because these are anchored to the walls via the papillary muscles. The larger end-systolic size and possibly altered LV shape could also result in malorientation of the papillary muscles, which in turn could result in IMLC.

**Other Possible Influencing Factors**

The end-systolic mitral annular dimension in group 1 dogs was also closely related to the degree of MR. Normally, the sphincteric contraction of the posterior aspect of the mitral annulus helps seal the approximated rough edges of the mitral leaflets. Mitral annular dysfunction might result in poor sealing of the leaflets and thus cause MR. Mitral annular dysfunction in our dogs, however, occurred secondary to LV dysfunction. It is possible, however, that isolated posterobasal infarction could involve the active portion of the mitral annular sphincter and cause MR without being associated with global LV dysfunction.

The LV end-diastolic size also correlated well with the degree of MR in both our groups of dogs. We could not produce LV dysfunction in our experiments without also producing LV dilatation; with production of greater amounts of ischemia, there was greater LV dilatation. The relation between the degree of MR and LV end-diastolic size may, therefore, simply reflect the relation between MR and LV dysfunction. On the other hand, the LV end-diastolic size may have independently influenced the amount of MR by changing LV shape and causing malorientation of the papillary muscles.

The end-systolic LA size also correlated linearly with the degree of MR in group 1 dogs where the LA
size was measured. The increase in LA size could have occurred secondary to both the degree of MR and the degree of LV dysfunction (increase in LV filling pressures). It is interesting to note that although we used an acute model of ischemic MR, we observed significant changes in mitral annular, LA, and LV dimensions, probably because during baseline these animals were working at the low end of their LA and LV volumes. Reduction in LM artery flow could also have resulted in ischemia and dilatation of all left heart structures.

Study Limitations

We measured papillary muscle thickening by using two-dimensional echocardiography. It could be argued that the sampling rate of 30 frames per second at heart rates of 120–150 beats/min may not be optimal for precisely assessing thickening. To overcome this possible limitation, we estimated thickening of the papillary muscles during three consecutive cycles and derived mean values from these data. Regional wall thickening has also been studied in extensive detail using two-dimensional echocardiography, and a close correlation between this technique and the higher-resolution technique of sonomicrometer crystals has been demonstrated previously.30

The motion of the heart could also have induced errors. The heart rotates along its long axis during each cardiac cycle. A region of the heart imaged in diastole may not be represented along the same long axis during systole.31 To overcome this limitation, the papillary muscles were imaged in their short axes, where their measurement would not be affected by this specific motion artifact. Similarly, during each cardiac cycle, the base of the heart moves cephalad. A region of the heart imaged during diastole may not be represented along the same short axis during systole.31 To overcome this limitation, the papillary muscles were also imaged along their long axis, where their measurement would not be affected by this motion artifact. Averaging the measurements from both the short- and long-axis views in group 3 dogs probably reduced the errors produced by using either view alone.

The inhomogeneity of flow to the anterior papillary muscles could also result in inhomogeneity of papillary muscle thickening. It could thus be argued that the reason we did not see mitral valve prolapse in our models is that parts of the papillary muscles could be thickening adequately, thus preventing prolapse from occurring. In group 3 dogs, we demonstrated that the inhomogeneity in flow does not result in inhomogeneity in papillary muscle thickening. Occlusion of flow to the papillary muscles results in paralysis of the entire muscle without resultant mitral valve prolapse.

Although the worst MR was noted in our models during severe reduction in LV function, which would not be compatible with life, considerable MR was also noted in the presence of either moderate reduction in global LV function or reduction in LV function induced by ischemia involving large regions of the LV. These latter instances more closely resemble the clinical situation and the amount of MR usually seen in patients with chronic coronary artery disease and reduced LV function. Severe reduction in LV function during global ischemia in our experiments was related to reduced LM artery flow, a condition not usually seen in the clinical setting.

Possible Clinical Implications

Historically, patients with ischemic MR undergoing coronary artery bypass grafting have also undergone mitral valve replacement. The prognosis in such patients has been related to LV function at the time of surgery.32 A significant number of such patients have reversible ischemic dysfunction, allowing improvement in LV function after surgery.33 If MR is related to reduced global LV function secondary to ischemia, it should also reverse after revascularization, as has been reported in an uncontrolled study.34

Based on our data, we would speculate that patients with coronary artery disease, poor LV function, and MR, in whom ischemia can be demonstrated using techniques such as thallium-201 imaging,35 may not need to undergo valve replacement unless the mitral apparatus itself is structurally damaged. Because the mitral annulus is usually enlarged in such patients, a limited form of valve repair, such as annuloplasty with or without ring placement, may be desirable. Such an approach would remove the risk of increased operative mortality associated with mitral valve replacement as well as the long-term consequences of having a prosthetic valve, and it could also have a beneficial effect on preserving LV function by maintaining an intact mitral apparatus.36

Conclusions

In this study, we have demonstrated that ischemia and dysfunction of either one or both papillary muscles and the adjacent regions of the LV myocardium from where the muscles arise does not result in MR. MR occurs only when significant global LV dysfunction is produced either by regional or global ischemia. The term “papillary muscle dysfunction” should, therefore, be discarded when describing MR in patients with coronary artery disease and poor LV function. MR in this setting is invariably associated with IMMC and never with mitral valve prolapse. These findings shed new light on the mechanism of ischemic MR and may have important clinical implications.

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