Infarct Restraint Attenuates Remodeling and Reduces Chronic Ischemic Mitral Regurgitation After Postero-Lateral Infarction

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Background. **Chronic ischemic mitral regurgitation (IMR) is produced by adverse postinfarction ventricular remodeling. We hypothesize that restraining infarct expansion reduces left-ventricular (LV) dilatation and the severity of mitral regurgitation.**

Methods. **Two groups of 6 sheep had coronary snares placed around the second and third obtuse marginal coronary arteries and four piezoelectric transducers sutured within myocardium across the mid short axis of the LV. In one group, a patch of Marlex mesh was precisely fitted and lightly sutured to myocardium destined for infarction (determined by temporary snare occlusion). Two weeks after instrumentation, coronary snares were tied tight to infarct approximately 24% of the postero-lateral LV mass. Transdiaphragmatic echocardiograms were obtained in all animals at baseline, and 30 minutes, and 2, 5, and 8 weeks after infarction.**

Results. **Echocardiograms confirmed similar infarct sizes and locations in both groups. Eight weeks after infarction, IMR grade averaged 3.6+ (scale: 0, no MR; 4, severe MR) in control sheep and 1.9+ in mesh-restrained animals ($p = 0.0001$). LV end-diastolic and end-systolic volumes at the eighth week were less in mesh-treated sheep (87 ± 11.3 vs 113 ± 18.3; 61 ± 10.6 vs 77 ± 14.1, respectively), but differences were not significant. Data from mid short axis piezoelectric transducers indicated significantly less strain in the infarcted myocardium in mesh-restrained sheep than in control.**

Conclusions. **Early restraint of postero-lateral infarct expansion attenuates the severity of ischemic mitral regurgitation and slows ventricular dilatation. However, the remodeling process is not arrested 8 weeks after infarction.**

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Ischemic mitral regurgitation is mitral insufficiency caused by partial or complete obstruction of one or more coronary arteries [1]. The valve leaflets and subvalvular apparatus are normal. Yet, the valve leaks, often massively. Ischemic mitral regurgitation (IMR) most often develops progressively over time after an inferior wall myocardial infarction (MI) as the postinfarction ventricle remodels.

Coronary artery disease (CAD) now accounts for approximately 70% of the 550,000 patients with congestive heart failure (CHF) in the United States [2]. The prevalence of postinfarction IMR (2+ or greater) is estimated to be 7.2% of all patients who have cardiac catheterization for symptomatic coronary artery disease [3]. After acute myocardial infarction, the multicenter Survival and Ventricular Enlargement (SAVE) trial demonstrated conclusively that any degree of mitral regurgitation more than doubles the mortality compared with patients without MR within 3.5 years [4, 5].

Recent large studies by Gillinov and Grossi and associates attempted to assess the relative efficacy of mitral valve repair and replacement in patients with IMR [6, 7]. These studies meticulously excluded patients with coronary arterial disease and mitral disease of nonischemic origin. Whereas both techniques were generally successful in eliminating MR, the 5-year mortality associated with either operation approached 50% [6–8]. The most significant point in both these manuscripts, which was emphasized by Miller in his associated editorial [8], is that the 5-year survival of all patients approached 50%, whether the valve was repaired or replaced. This mortality at 5 years is very close to that expected for the medically managed CHF population in general [9]. The surgical results indicate that elimination of IMR does not appreciably alter the natural history of CHF and suggests that IMR is a sign of adverse remodeling rather than a precipitating cause.

Adverse remodeling after MI is initiated by acute infarct expansion, which results in a progressive myopathic process in normally perfused myocardium [10, 11].

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This process is difficult to reverse by medical or surgical means; however, we have demonstrated in an ovine model of left-ventricular aneurysm that adverse remodeling can be reduced and CHF averted by stiffening the infarct and restraining infarct expansion [12].

These clinical and experimental data have led to the hypothesis that IMR is a manifestation of a ventricular disease process, termed "ventricular remodeling," and that elimination of IMR does not significantly alter the progressive nature of this process. This study tests the hypothesis that restraining acute infarct expansion preserves ventricular geometry, attenuates ventricular dilatation, and reduces the development of IMR in an ovine model of acute postero-lateral infarction that consistently progresses to severe IMR and CHF [13].

Material and Methods

Surgical Protocol

In compliance with the Guide for the Care and Use of Laboratory Animals published by the National Institutes of Health (National Institutes of Health publication 85-23, revised 1985) 12 Dorsett hybrid sheep between 35 and 45 kg and bred for laboratory use (Animal Biotech Industries, Doylestown, PA) were induced with sodium thiopental (12.5 mg/kg intravenously) and intubated. Anesthesia was maintained with 1% to 2% isoflurane in oxygen. All animals received glycopyrrolate (0.4 mg intravenously) and enrofloxin (10 mg/kg, IV) 1 hour before incision.

All animals underwent left thoracotomy with aseptic technique. Polypropylene snares were placed loosely around the second (OM2) and third (OM3) obtuse marginal branches of the left circumflex coronary artery [12, 13]. Group assignment was random. In addition to the described initial instrumentation performed in the 6 control animals, 6 animals (mesh group) underwent placement of a patch of Marlex mesh, a nonabsorbable, monofilament, polypropylene mesh, sutured over the precise location of the posterior infarction as demonstrated by brief tightening of the coronary snares to produce blanching of the infarct territory (Fig 1).

Coronary snares were passed through pressure tubing and placed in a subcutaneous pocket. The thoracotomy was closed in layers. The left chest was drained with a single chest tube introduced through a separate stab incision. After emergence from anesthesia, the chest tube and endotracheal tube were removed. Animals received buphrenorphine (5 μg/kg) just before extubation and flunixin meglumine (1 mg/kg) for postoperative pain relief. Enrofloxacin (10 mg/kg intramuscularly) was administered on postoperative days 1 and 2.

Baseline Data

Ten to 14 days after initial instrumentation, sheep were induced with sodium thiopental (12.5 mg/kg intravenously) and intubated. Anesthesia was maintained with 1% to 2% isoflurane in oxygen. The surface electrocardiogram (ECG) and arterial blood pressure were continuously monitored (Sonometrics Inc., London, Ontario, Canada) and recorded during all data collection procedures. A high-fidelity pressure transducer (Spc-350; Millar Instruments Inc., Houston, TX) was inserted from the femoral artery into the left ventricle (LV) for continuous LV pressure (LVP) monitoring (78534c monitor; Hewlett-Packard, Palo Alto, CA). A pulmonary artery catheter (131-hour, 7fr; Baxter Healthcare Corp, Deerfield, IL) was also placed for each data collection procedure. Thermodilution cardiac output was measured in triplicate at each serial time point for each animal. Animals were disconnected from the ventilator and atrially paced at 120 bpm for all measurements and echocardiograms.

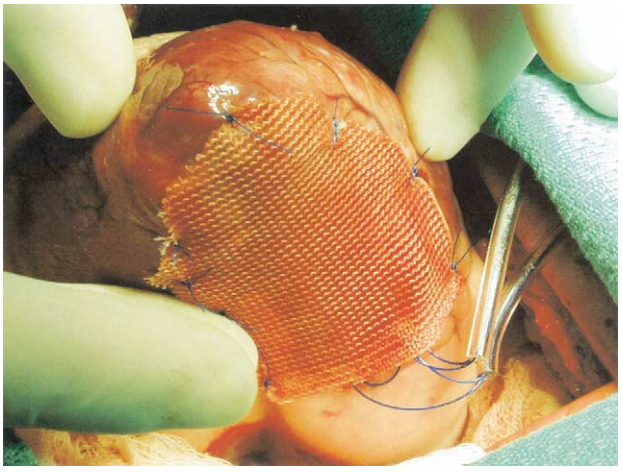

Fig 1. Intraoperative photograph demonstrating placement of Marlex mesh restraint patch over posterolateral infarct territory. The base of the heart is at the bottom, the posterior descending artery is at the left, and the apex is at the top.

Echocardiography

Quantitative two-dimensional subdiaphragmatic echocardiograms were obtained before infarction and at 30 minutes, and 2, 5, and 8 weeks after infarction [12]. A sterile midline laparotomy or right or left subcostal incisions were made and subdiaphragmatic two-dimensional echocardiographic images were obtained using a 5-MHz. probe (77020A; Hewlett Packard). Images were recorded on 0.5-inch videotape at 30 Hz (Panasonic AG-6300 VHS Recorder; Matsushita Electrical Ind. Co Ltd, Osaka, Japan). Left ventricular short axis images at three levels (at the tips of the papillary muscles, at the bases of the papillary muscles and at the apex) and two orthogonal long axis views were obtained. Previous reports have validated the reproducibility and effectiveness of this technique for evaluating LV remodeling in sheep [12].

Left ventricular volumes at end-systole and end-diastole were calculated using Simpson's rule [14]. Ejection fraction (EF) was calculated as the ratio of the difference of end-diastolic and end-systolic volumes to the end-diastolic volume.

Degree of mitral regurgitation (MR) was graded in a semiquantitative fashion with a scale of 0 to 4, with 0

Table 1. Hemodynamic Data

	MAP (mm Hg)	LVEDP (mm Hg)	CVP (mm Hg)	PADP (mm Hg)	CO (L/min)
Control Group					
Preinfarct	101.2 ± 9.6	3.8 ± 4.1	11.8 ± 2.7	19.8 ± 4.97	3.79 ± 0.89
Postinfarct	87 ± 11.8	5.2 ± 3.6	13.8 ± 5.1	21.6 ± 8.0	3.92 ± 1.32
2 weeks	99 ± 12.0	4.2 ± 2.2	11.6 ± 5.4	18.8 ± 6.6	3.65 ± 0.56
5 weeks	103 ± 8.7	2.6 ± 1.3	9.8 ± 4.8	16.0 ± 3.1	3.45 ± 0.74
8 weeks	103 ± 24.3	4.0 ± 1.6	10.4 ± 5.0	15.8 ± 3.8	3.64 ± 0.94
Mesh Group					
Preinfarct	94.3 ± 8.6	6.0 ± 2.9	16.8 ± 2.8	21 ± 2.7	3.86 ± 0.94
Postinfarct	94.0 ± 20.8	5.8 ± 2.4	20.3 ± 2.8	24.5 ± 10.2	4.14 ± 0.25
2 weeks	98.9 ± 12.0	6.5 ± 3.1	16.5 ± 2.1	21.3 ± 5.7	3.41 ± 0.85
5 weeks	90.42 ± 29.9	7.0 ± 2.6	16.5 ± 1.3	20.7 ± 1.5	3.83 ± 0.38
8 weeks	108 ± 9.4	8.5 ± 1.3	18.0 ± 2.2	20.5 ± 5.0	4.15 ± 0.76

Summary of changes in mean arterial pressure (MAP), left ventricular end-diastolic pressure (LVEDP), central venous pressure (CVP), pulmonary artery diastolic pressure (PADP), and cardiac output (CO). Only central venous pressure differed significantly between groups, $p = 0.001$.

representing no MR and 4 representing severe MR based on the size and geometry of the regurgitant jet.

Sonomicrometry Array Localization

As previously described, sonomicrometry array localization (SAL) is an imaging technique that utilizes small piezoelectric transducers to permanently label specific locations of myocardium [15, 16]. In the present study, four transducers (2 mm in diameter) were inserted into the myocardium of the LV free wall. Transducers were sutured in the midmyocardium along the mid left ventricular short axis at the left anterior descending (LAD) coronary artery, the medial and lateral edges of the infarct region, and at a point half the distance from the LAD to the medial edge of the planned infarct. This transducer array allows circumferential strain measurements of three intertransducer segments representing remote myocardium, borderzone myocardium adjacent to the infarct, and the infarct.

Time-of-flight measurements of the distance between all pairs of transducers were made once every 5 ms, in real time, using a custom data acquisition system from Sonometrics Incorporated (London, Ontario, Canada). Sonomicrometry data were recorded at all serial time points during remodeling. End-diastolic distances obtained from sonomicrometry at each postinfarction timepoint were normalized to the baseline measurements (before infarction) for the same segment lengths to yield a percent change in ED segment length. The percent change in segment lengths was an indicator of regional strain.

Infarction

After baseline hemodynamic, echocardiographic, and sonometric data were recorded, the previously placed subcutaneous snares were exposed, tightened, and tied to produce the infarction. Each animal received magnesium sulfate (1 g intravenously), bretylium (10 mg/kg intravenously), and lidocaine (3 mg/kg intravenous bolus followed by 2-mg/min infusion) before infarction. Hemodynamic, echocardiographic, and sonometric data were again collected 30 minutes after infarction.

Follow-Up Studies

Sonomicrometry, hemodynamic, and echocardiographic data were collected at 30 minutes and 2, 5, and 8 weeks after infarction. After the 8-week study, the animal was euthanized (80 meq potassium chloride). The heart was excised and photographed to establish infarction size and location and to confirm the position of the sonomicrometry transducers.

Statistics

Measurements are reported as means ± standard deviation. Differences between groups are compared by two-way analysis of variance with the Bonferroni correction for repeated measures (SPSS, Chicago, IL). Differences in degree of mitral regurgitation were compared using the Mann-Whitney test.

Results

Hemodynamic Data

Hemodynamic data are summarized in Table 1. No significant differences in left-ventricular end-diastolic pressure, pulmonary artery diastolic pressure, mean arterial pressure, or cardiac output were observed between groups. Central venous pressures were significantly greater in mesh-restrained sheep ($p = 0.001$).

Echocardiographic Data

Echocardiographic data are summarized in Table 2. Immediate postinfarction echocardiograms and gross examination of hearts explanted at the end of the study confirmed similar size and location of infarction between groups [13]. LV end-diastolic volume (LVEDV), whereas similar between groups at baseline, is greater in control animals: 113 ± 18.3 as compared with the mesh-restrained sheep, 87 ± 11.3 ($p = 0.08$) (Fig 2). A similar trend is seen in the LV end-systolic volumes (LVESV), with control animals having a mean LVESV of 77 ± 14.1 8 weeks after infarction as compared with 61 ± 10.6 for the mesh group ($p = 0.12$) (Fig 3). Within-groups LVEDV significantly increases over the 8 weeks after infarction

Table 2. Echocardiographic Data

	LVEDV (cc)[a]	LVESV (cc)[b]	EF	MR Grade[c]
Control Group				
Preinfarct	56 ± 9.8	33 ± 6.4	42.8 ± 3.4	0.4
Postinfarct	76 ± 10.7	46 ± 13.0	46.0 ± 12.8	2.2
2 weeks	85 ± 8.8	58 ± 11.3	37.2 ± 10.2	3.0
5 weeks	94 ± 6.0	67 ± 7.5	28.6 ± 7.4	3.3
8 weeks	113 ± 18.3[d]	77 ± 14.1[e]	31.3 ± 7.0	3.6
Mesh Group				
Preinfarct	60 ± 11.8	34 ± 10.3	45.6 ± 7.3	0.5
Postinfarct	69 ± 16.5	40 ± 10.3	45.6 ± 7.8	0.8
2 weeks	77 ± 15.3	50 ± 12.2	35.1 ± 13.2	1.0
5 weeks	79 ± 8.7	58 ± 7.6	26.0 ± 2.6	1.7
8 weeks	87 ± 11.3[f]	61 ± 10.6[g]	30.6 ± 3.9	1.9

Summary of changes in left-ventricular end-diastolic volumes (LVEDV), left-ventricular end-systolic volumes (LVESV), ejection fraction (EF), grade of mitral regurgitation (MR Grade), and diastolic muscle to cavity area ratio.

[a] $p = 0.08$ between groups; [b] $p = 0.12$ between groups; [c] $p = 0.0001$ between groups; [d] $p = 0.0001$ preinfarct compared with 8 weeks; [e] $p = 0.001$ preinfarct compared with 8 weeks; [f] $p = 0.015$ preinfarct compared with 8 weeks; [g] $p = 0.010$ preinfarct compared with 8 weeks.

(control, $p = 0.0001$; mesh, $p = 0.015$). LVEDV also increases during remodeling (control, $p = 0.001$; mesh, $p = 0.01$). The increase in diastolic volume compared with before infarction achieves statistical significance at 30 minutes postinfarction in control animals, but does not reach significance until 5 weeks postinfarction in mesh-restrained sheep.

Ejection fraction, while decreasing in both groups, did not differ significantly between groups at the 8-week timepoint.

Whereas both groups had a similar degree of MR at base line, 0.4+ in control animals and 0.5+ in mesh-treated animals, the increase in MR grade was higher at 8 weeks in the control group, 3.6+ as compared with the mesh group, 1.9+ (Fig 4). The difference in the severity of MR between groups is significant ($p = 0.0001$) and was apparent 30 minutes after infarction.

Sonomicrometry Data

Sonomicrometry data comparing 8-week postinfarction end-diastolic segment length with baseline values are summarized in Table 3. End-diastolic segment lengths were lower in all regions in the mesh group, with the difference in percent change in ED length achieving statistical significance in the infarct region (29.6% increase in ED length in control group vs 2.4% increase in mesh group, $p = 0.049$).

Comment

A patch of Marlex mesh applied before infarction overcomes the technical obstacle of restraining infarct expansion by eliminating the need for reoperation at the time of infarction. Consistency of ovine coronary arterial anatomy between sheep and lack of preformed collateral vessels permit accurate prediction of infarct size and location and precise fitting of the mesh over the planned infarction. The mesh becomes incorporated into the epicardial layer during the interval before infarction [12]. The method obviously has no therapeutic value, but was used as an experimental device to stiffen the material

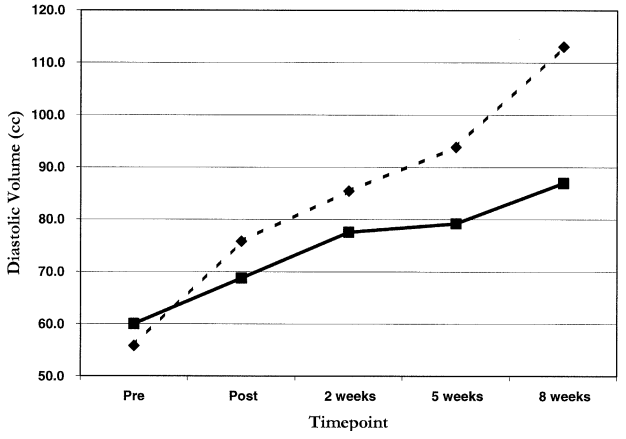

Fig 2. Diastolic volume (cc) in control group (dashed line). *Mesh group* (solid line). p ≤ *0.05 at 5 weeks between groups;* p ≤ *0.005 at 8 weeks between groups.*

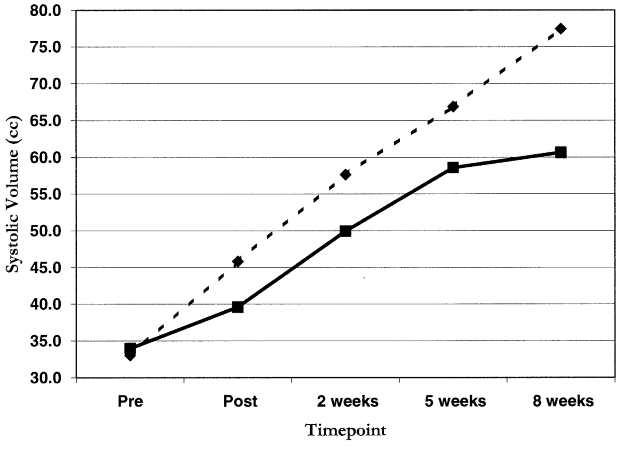

Fig 3. Systolic volume (cc) in control group (dashed line). *Mesh group* (solid line). p ≤ *0.05 at 5 weeks between groups;* p ≤ *0.005 at 8 weeks between groups.*

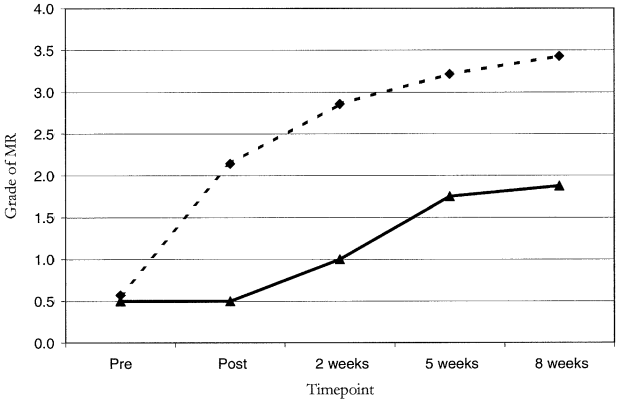

Fig 4. Degree of mitral regurgitation (MR) graded on a scale of 0 to 4 (0 = no MR, 4 = severe MR) in control group (dashed line) *and mesh group* (solid line). $p \leq 0.05$ *at postinfarction and 2 weeks between groups;* $p \leq 0.005$ *at 5 and 8 weeks between groups.*

properties of the infarct [12]. This permitted a test of our hypothesis.

The preplaced patch, confined to just the area of infarction, stiffened the material properties of the infarct and essentially prevented infarct expansion as compared with the expansion that occurred in control animals. Although expansion of viable, peri-infarct, borderzone myocardium was less than control in mesh-treated animals, substantial expansion nevertheless occurred during remodeling despite preventing expansion of the infarct. This result was not expected; instead, we expected that stress and strain in borderzone myocardium of mesh-treated animals would approximate that in remote myocardium and that the remodeling process would decrease and eventually stop.

The sonomicrometry data suggest that postinfarction expansion is similar in the infarct and peri-infarct borderzone myocardium in control animals. These data emphasize the importance of fully perfused borderzone myocardium in the remodeling process and the fact that strain is as great in this region as it is in the infarct itself. Although our study is underpowered to show significant differences in volume changes and regional expansion of borderzone and remote myocardium between groups, the trends strongly suggest that the material properties of the borderzone must also be stiffened to arrest the remodeling process and to produce a compensated, stable ventricle. A larger patch to include a rim of viable peri-infarct borderzone myocardium may successfully prevent development of MR and arrest the postinfarction remodeling process after the initial, immediate increase in ventricular volume that occurs immediately after the infarct. This hypothesis awaits testing.

Table 3. Sonometric Data: End-Diastolic Length Percent Change at 8 Weeks Versus Baseline

Group	Remote	Peri-Infarct	Infarct
Control	17.81%	39.23%	29.57%[a]
Mesh	12.30%	20.97%	2.43%[a]

Summary of percent change compared with baseline in end-diastolic intertransducer distances measured from transducers spanning infarct, periinfarct, and remote regions of myocardium.

[a] $p = 0.049$ between groups.

Doctor Benjamin Jackson, working in our laboratory, has shown that expansion (stretching) of a transmural MI initiates a progressive myopathic process in normally perfused myocardium [11]. This phenomenon is initially localized to myocardium immediately adjacent to the infarct but extends during the remodeling process to convert contiguous normally perfused myocardium into hypocontractile, remodeled myocardium [10, 11]. Using contrast echocardiography, Jackson has demonstrated that remodeled myocardium is associated with increased regional wall stress in the borderzone region adjacent to an infarct early after transmural myocardial infarctions.

For this study, we hypothesized that restraint of infarct expansion using Marlex mesh would reduce myocardial wall stress and strain in borderzone myocardium. We speculated that reduction in borderzone stress would arrest the formation of remodeled myocardium and produce a compensated, stable ventricle. As our results show, follow-up beyond 8 weeks and more definitive regional strain and biochemical analyses are necessary to answer this very important question.

Central venous pressure was the only hemodynamic variable that differed significantly between groups. The cause of this is uncertain but may be the result of a pericardial inflammatory response initiated by the mesh. Ejection fraction was similar between groups in spite of the increased degree of MR in the control animals. This finding would suggest that the contractile performance of the mesh-treated ventricles is superior to that of the controls.

These clinical and experimental data lead to the disturbing possibility that elimination of chronic IMR is of limited value in reversing the remodeling process and treating established CHF. The corollary of this conclusion is that interventions should occur before remodeling in an effort to interrupt the myopathic element of the remodeling process. The most promising, currently available surgical strategies to accomplish this are direct infarct restraint or infarct reperfusion [12, 17]. Effective pharmacologic interventions may also be developed as the biochemical, cellular, and genetic characteristics of remodeled myocardium and the myopathic process are elucidated.

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DISCUSSION

DR VERDI J. DISESA (West Chester, PA): Can you tell us a little bit more about the nature of the mitral insufficiency in these animals. Was it an eccentric jet characteristic of a restricted motion posterior leaflet like we see clinically with these kinds of infarcts? Or was it more of a central jet with annular dilatation that might be due to the global enlargement of the ventricle. This may help us to understand a little bit better how your constraining patch was affecting the mitral valve.

DR MOAINIE: This model that was developed in our laboratory several years ago was developed to emulate the chronic ischemic mitral regurgitation, which results from tethering of the posterior leaflet, and it does result in an eccentric jet. Our hypothesis is that the way the patch is attenuating this is by restraining the posterior displacement of the left ventricular wall, thus keeping the posterior leaflet from moving away by keeping the posterior wall closer to the annulus.

DR JAI S. RAMAN (Melbourne, Australia): We did all the initial work with ventricular containment with what is now called the Acorn cardiac support device. At that stage, we used custom-made mesh, which evolved from polyester hernia meshes. One of the concerns that was always raised was diastolic dysfunction might be expected with a procedure of this nature. And even with the present generation of cardiac support device in the experimental setting, some amount of diastolic dysfunction may exist. Did you look at remote diastolic dysfunction or global diastolic dysfunction with your technique of localized inferior wall restraint? I did not see that specifically addressed in your presentation.

DR MOAINIE: Certainly, the concern with any type of restraint device has always been adversely affecting diastolic function, and that was the reason that we used this partial restraint; it really spares the vast majority of the left ventricle and totally spares the right ventricle, and thus, diastolic dysfunction was less of an issue. We specifically evaluated for it in our echocardiograms and saw no evidence of diastolic dysfunction throughout the study.

DR RALPH J. DAMIANO, JR. (St. Louis, MO): I have two questions for you. First of all, the infarct restraint appeared to ameliorate the remodeling process, but certainly not prevent it. I would like to know if you could speculate for us on strategies to further prevent the progressive remodeling. Clearly, there appears to be progressive increase in volumes, mitral regurgitation, and changes in the muscle ratio in the restraint group.

Second, I would like you to tell us your thoughts on the eventual clinical implications of your work.

DR MOAINIE: In answer to your first question, I think the remodeling process is a multifaceted process that occurs in response to an infarction. It is partially a mechanical process and partially a biochemical process. And as a result, I think it requires a multimodal therapy involving not just mechanical alteration to attenuate the ventricular remodeling process, but also medical therapies to attenuate the biochemical physiology that is going on that is resulting in that remodeling. And that is an area that is of extreme interest to us in the lab at present.

One of the current projects that we are working on is looking at restraining the entire LV, going from the posterior descending artery to the left anterior descending, to see if that would improve our results in terms of decreasing the amount of dilatation even more so than just an isolated patch.

In terms of the future applications of this research, I would foresee that if future clinical trials of this are supportive of our results, that a patient presenting with an acute infarction of the posterolateral wall, knowing that that infarction is ultimately going to progress to chronic ischemic mitral regurgitation, they would at the time of their CABG also undergo placement of an infarct restraint device.