Pathogenesis of Mitral Regurgitation in Tachycardia-Induced Cardiomyopathy

Tomasz A. Timek, MD; Paul Dagum, MD, PhD; David T. Lai, FRACS; David Liang, MD, PhD; George T. Daughters, MS; Neil B. Ingels, Jr, PhD; D. Craig Miller, MD

Background—Dilated cardiomyopathy is often associated with mitral regurgitation (MR), or so-called functional MR, the mechanism of which continues to be debated. We studied the valvular and ventricular 3D geometric perturbations associated with MR in an ovine model of tachycardia-induced cardiomyopathy (TIC).

Methods and Results—Nine sheep underwent myocardial marker implantation in the left ventricle (LV), mitral annulus, and mitral leaflets. After 5 to 8 days, the animals were studied with biplane videofluoroscopy (baseline), and mitral competence was assessed by transesophageal echocardiography. Rapid ventricular pacing (180 to 230 bpm) was subsequently initiated for 15±6 days until the development of TIC and MR, whereupon biplane videofluoroscopy and transesophageal echocardiography studies were repeated. LV volume was calculated from the epicardial marker array. Valve closure time was defined as the time after end diastole when the distance between leaflet edge markers reached its minimal plateau. TIC resulted in increased LV end-diastolic volume (P=0.001) and LV end-systolic volume (P=0.0001) and greater LV sphericity (P=0.02). MR increased significantly (grade 0.2±0.3 versus 2.2±0.9, P=0.0001), as did mitral annulus area (817±146 versus 1100±161 mm², P=0.0001) and mitral annulus septal-lateral diameter (28.2±3.5 versus 35.1±2.6 mm, P=0.0001). Time of valve closure (70±18 versus 87±14 ms, P=0.23) and angular displacement of both the anterior (29±5° versus 27±3°, P=0.3) and posterior (55±15° versus 44±11°, P=0.13) leaflet edges relative to the mitral annulus after valve closure did not change, but leaflet edge separation after closure increased (5.2±0.9 versus 6.8±1.2 mm, P=0.019).

Conclusions—MR in TIC resulted from decreased leaflet coaptation secondary to annular dilatation in the septal-lateral direction. These data support the use of annular reduction procedures, such as rigid, complete ring annuloplasty, to address functional MR in patients with dilated cardiomyopathy. (Circulation. 2001;104[suppl I]:I-47-I-53.)

Key Words: mitral valve • regurgitation • cardiomyopathy • pacing

Significant mitral regurgitation (MR) is often present in patients with dilated cardiomyopathy and portends poor long-term outcome.1–3 Recently, innovative surgical techniques have been implemented, both clinically and experimentally, to improve cardiac function and valvular competence in end-stage heart failure. These include the Batista procedure,4 passive cardiac constraint,5,6 cardiomyoplasty,7 and mitral valve repair.8 Mitral valve repair, in particular, has yielded encouraging midterm results in this patient population, significantly improving survival8,9; however, the optimal surgical correction in these patients is yet to be defined because the valves are structurally intact and the pathogenesis of the MR is incompletely understood. The development of “functional” mitral incompetence in cardiomyopathic hearts has been attributed to altered left ventricular (LV) chamber geometry,10,11 papillary muscle tethering,12,13 annular dilatation,14 and decreased LV systolic function,15 yet the precise mechanism remains elusive. Therefore, insight into the mechanism of functional MR may bring to fruition more rational surgical approaches for the restoration of valve competence.

Animal models of end-stage cardiomyopathy, produced by either rapid pacing5,16,17 or microembolization,10 have contributed to the understanding of the clinical entity. Because these animals also develop MR,5,10 an opportunity is provided to study mitral incompetence in dilated cardiomyopathy. Using the myocardial marker method in an ovine model, we studied the precise 3D perturbations of ventricular and valvular geometry associated with the development of tachycardia-induced cardiomyopathy (TIC) and MR.

Methods

Surgical Preparation

The surgical preparation for myocardial marker insertion has been described in detail previously,18 so it will be summarized only briefly here. Nine adult sheep were premedicated with ketamine (25 mg/kg

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Circulation is available at http://www.circulationaha.org

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IM) for venous and arterial line placement and were monitored, and anesthesia was induced with sodium thiopental (6.8 mg/kg IV). The animals were intubated and mechanically ventilated (Servo Anesthesia Ventilator, Siemens-Elema AB), and anesthesia was maintained with inhalational isofluorane (1% to 2.2%). A left thoracotomy was performed, and the heart was suspended in a pericardial cradle. Eight tantalum myocardial markers (No. 2, 3, 5, 6, 9, 10, 12, 13, Figure 1A; inner diameter, 0.8 mm; outer diameter, 1.3 mm; length, 1.5 to 3.0 mm) were inserted beneath the LV epicardial surface along 4 equally spaced longitudinal meridians for LV volume determinations with 1 marker (No. 1) placed at the LV apex. Three additional markers were inserted into the subendocardium corresponding to the subepicardial markers at the equatorial anterior, lateral, and posterior positions (not shown but just beneath markers 3, 10, and 13 in Figure 1A). The right atrium and descending thoracic aorta were cannulated after systemic heparinization (300 IU/kg). After establishment of cardiopulmonary bypass and after cardioplegic arrest, 8 tantalum markers were sutured to delineate the circumference of the mitral annulus (No. 15 through 22, Figure 1B), and 1 additional marker was sewn on each papillary muscle tip (No. 23 and 24, Figure 1A). Four markers were sewn along the central meridian of the anterior leaflet (No. 32 through 35, Figure 1B), and 2 were sewn along the central meridian of the posterior leaflet (No. 36 and 37, Figure 1B). The animal was rewarmed, its atriotomy closed, and the cross clamp removed, and after resuscitation, the sheep was weaned from bypass. A micromanometer pressure transducer (PA4-S-X6, Konigsberg Instruments, Inc.) was placed in the LV chamber through the apex. A monopolar pacing lead was sewn onto the anterior LV wall.

**Experimental Protocol**

After 6 ± 1 (mean ± SD) days, each animal was taken to the cardiac catheterization laboratory, sedated with ketamine (1 to 4 mg · kg⁻¹ · h⁻¹ IV infusion) and diazepam (5-mg IV bolus as needed), intubated, and mechanically ventilated (veterinary anesthesia ventilator 2000, Halowell EMC). Esmolol (20 to 50 µg · kg⁻¹ · min⁻¹ IV) and atropine sulfate (0.01 mg · kg⁻¹ · min⁻¹ IV) infusions were used to minimize reflex sympathetic and parasympathetic responses. Simultaneous biplane videofluoroscopy and hemodynamic data recordings were obtained during stable steady-state conditions. Transesophageal Doppler echocardiography was performed by an experienced echocardiographer during acquisition runs to assess MR. The MR was graded according to the extent and width of the regurgitant jet by an experienced echocardiographer (Dr Liang) and categorized as none (0), mild (1), moderate (2), moderate to severe (3), or severe (4).

**Data Acquisition**

Images were acquired with the animal in the right lateral decubitus position with a Phillips Optimus 2000 biplane Lateral ARC 2/Poly DIAGNOST C2 system (Phillips Medical Systems, North America) with the image magnification set in the 9” fluoroscopic mode. Marker image positions from the 2 simultaneous radiographic views were digitized and merged to yield 3D coordinates for each radiopaque marker every 16.7 ms with custom-designed software. Synchronized ascending thoracic aortic pressure, LV pressure, and ECG voltage signals were recorded simultaneously during videographic data acquisition.

**Pacing Protocol**

After data acquisition, while the animals were still sedated, a rapid-pacing pulse generator (Prodigy S 8164, Medtronic Medical) was inserted into a subcutaneous pocket and connected to the previously externalized monopolar lead, and the animal was recovered. Rapid pacing was initiated 24 hours later. During the pacing period, interval transthoracic echocardiography was performed to assess LV dimensions, systolic LV performance, and MR (with the pacer off) to guide pacing rate adjustments. The end point for cessation of pacing was development of significant MR and TIC. The first 2 animals were paced at 180 bpm and subsequent animals at 230 bpm, which resulted in faster development of heart failure and MR. The average period of pacing was 15 ± 6 days. After completion of the pacing protocol, the animals were returned to the catheterization laboratory with the pacer turned off before the study. Hemodynamic, marker, and echocardiographic data were again acquired as described above.

All animals received humane care in compliance with the Principles of Laboratory Animal Care formulated by the National Society for Medical Research and the Guide for Care and Use of Laboratory Animals prepared by the National Academy of Sciences and published by the National Institutes of Health (DHEW NIH publication 85-23, revised 1985). This study was approved by the Stanford Medical Center Laboratory Research Animal Review Committee and conducted according to Stanford University policy.

**Data Analysis**

**Timing Markers**

Three consecutive steady-state beats during normal sinus rhythm before and after rapid pacing were averaged and defined as baseline and TIC data for each animal. During each cardiac cycle, the time of end systole was defined as the videofluoroscopic frame containing the point of peak negative LV rate of pressure fall (−dP/dt), whereas the time of end diastole (ED) was defined as the image frame containing the peak of the ECG R-wave. Instantaneous LV volume was calculated from the epicardial LV markers with the use of a space-filling multiple tetrahedral volume method for each frame, ie, every 16.7 ms. Although myocardial volume is included in this calculated (overestimated) LV volume, it accurately reflects relative changes in LV chamber size. Stroke volume (SV) was calculated as the difference between end-diastolic (EDV) and end-systolic (ESV) volumes (SV = EDV − ESV).

**LV Geometry**

Longitudinal LV diameter was calculated as the distance in 3D space between the midseptal annulus and LV apex (markers 22 and 1, Figure 1A). The septal-lateral and anterior-posterior LV diameters were computed as the distances between subepicardial marker pairs 6 and 10 and 3 and 13, respectively. LV sphericity was calculated as the longitudinal LV long-axis diameter divided by the septal-lateral minor axis diameter.

**Valvular Dynamics**

Mitral annular area was determined by first dividing the annulus into “pie slices” on the basis of the annular centroid; these slices were then summed to yield total annular area. The septal-lateral diameter of the annulus was calculated as distance between the 2 markers in the middle of the septal and posterior mitral annuli (markers 22 and 18, respectively, Figure 1B). Instantaneous leaflet edge separation was calculated by measuring the distance between leaflet edge markers 35 and 36 for each time frame, and the time of mitral valve closure was defined as the time when leaflet edge separation reached its minimal systolic plateau as evidenced by <5% deviation in leaflet edge separation for ≥3 consecutive time frames. Leaflet separation in the closed position was calculated as the mean distance between
leaflet edge markers over the 10 frames (167 ms) after valve closure. Angular position of the anterior leaflet edge was calculated as the angle ($\theta_{35}$) between anterior leaflet edge marker (No. 35), AML annular hinge point (No. 22), and midseptal (No. 22) and midlateral (No. 18) annuli. Posterior leaflet edge angular position ($U_{35}$) between posterior leaflet edge marker (No. 36) and PML and AML annular hinge points.

Statistical Analysis

All data are reported as mean±SD unless otherwise stated. Hemodynamic and marker-derived data from 3 consecutive steady-state beats were aligned at ED (t=0), and data from the 3 beats were averaged for each of the 9 animals. Because of the loss of leaflet edge markers over time during pacing, marker data from only 5 animals were available to determine valve closure times, leaflet separation distance, and leaflet angular motion. The data (time aligned at ED) were analyzed from 20 frames before to 20 frames after ED, thereby allowing evaluation of the studied variables over the entire cardiac cycle. Data were compared by use of Student's $t$ test for paired observations with the level of statistical significance set at $P<0.05$.

Results

The average animal weight was 79.4±10.3 kg; cardiopulmonary bypass time was 90±27 minutes; and aortic cross-clamp time was 55±7 minutes. Correct marker position was confirmed in all animals at postmortem examination. Hemodynamic variables before and after pacing are shown in Table 1. Pacing markedly increased end-systolic and ED LV size and ED pressure. These changes were consistent with development of TIC.

### TABLE 1. Hemodynamics

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>TIC</th>
<th>$t$</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR, bpm</td>
<td>102±16</td>
<td>115±18</td>
<td>0.15</td>
</tr>
<tr>
<td>$dP/dt$, mm Hg/s</td>
<td>1350±219</td>
<td>1162±374</td>
<td>0.29</td>
</tr>
<tr>
<td>EDV, mL</td>
<td>160±57</td>
<td>201±67</td>
<td>0.001</td>
</tr>
<tr>
<td>ESV, mL</td>
<td>128±45</td>
<td>168±55</td>
<td>0.0001</td>
</tr>
<tr>
<td>SV, mL</td>
<td>32±14</td>
<td>33±15</td>
<td>0.95</td>
</tr>
<tr>
<td>LVEDP, mm Hg</td>
<td>16±6</td>
<td>30±6</td>
<td>0.017</td>
</tr>
<tr>
<td>LVP, mm Hg</td>
<td>98±12</td>
<td>96±13</td>
<td>0.8</td>
</tr>
</tbody>
</table>

HR indicates heart rate; LVEDP, LV ED pressure; and LVP, maximum systolic LV pressure. Data shown are mean±SD.

LV Geometry

Changes in LV dimensions with rapid pacing are summarized in Table 2. After pacing, the LV dilated in the anterior-posterior dimension and even more so in the septal-lateral dimension, with the latter being significantly larger at both end systole and ED. Overall, the LV chamber became more spherical. Mitral annular area increased after pacing by 36±14% and 46±13% at ED and end systole, respectively. Similarly, the annular septal-lateral diameter increased 25±12% at ED and 29±10% at end systole after rapid pacing. The distance between the anterior and posterior papillary muscle tips also increased at both ED (29.9±4.2 versus 35.0±4.1 mm, $P=0.0002$) and end systole (23.9±3.7 versus 30.4±3.7 mm, $P=0.0002$), further illustrating significant LV dilatation in TIC. LV wall thinning also occurred: ED myocardial wall thickness, measured as the distance between epicardial and endocardial marker pairs, decreased significantly in the anterior (12.6±5.0 versus 9.3±5.1 mm, $P=0.002$), lateral (12.3±5.1 versus 10.7±6.5 mm, $P=0.034$), and posterior (11.4±3.8 versus 10.6±4.1 mm, $P=0.002$) LV walls. The 3D shape of the mitral annulus at end systole before and after cardiomyopathy is shown in Figure 3.

Mitral Regurgitation

Before pacing, 1 animal had mild MR, and 2 animals had trace MR; no MR was observed in the remaining animals. After pacing, 4 animals developed mild to moderate MR, 2 developed moderate MR, 2 had moderate to severe MR, and 1 had severe MR. Overall, MR grade increased from 0.2±0.3 to 2.2±0.9 ($P=0.0001$). By echo, cardiomyopathy was al-

### Table 2. LV Dimensions

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>TIC</th>
<th>$t$</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-D, mm</td>
<td>106.4±7.1</td>
<td>107.0±6.3</td>
<td>0.7</td>
</tr>
<tr>
<td>ES</td>
<td>100.4±5.2</td>
<td>104.3±5.6</td>
<td>0.0001</td>
</tr>
<tr>
<td>AP-D, mm</td>
<td>71.1±5.4</td>
<td>73.5±3.4</td>
<td>0.2</td>
</tr>
<tr>
<td>SL-D, mm</td>
<td>58.3±5.3</td>
<td>65.2±4.6</td>
<td>0.002</td>
</tr>
<tr>
<td>Sphericity</td>
<td>1.86±0.27</td>
<td>1.67±0.15</td>
<td>0.02</td>
</tr>
<tr>
<td>MAA, mm$^2$</td>
<td>817±146</td>
<td>1100±161</td>
<td>0.00001</td>
</tr>
<tr>
<td>MA SL-D, mm</td>
<td>28.2±3.5</td>
<td>35.1±2.6</td>
<td>0.00001</td>
</tr>
</tbody>
</table>

L-D indicates longitudinal LV diameter (from marker 1 to 22); AP-D, anterior-posterior LV diameter (from marker 3 to 13); SL-D, septal-lateral LV diameter (from marker 6 to 10); sphericity, L-D/SL-D; MAA, mitral annular area; and MA SL-D, mitral annular septal-lateral diameter (marker 22 to 18). Data shown at ED and end systole (ES) as mean±SD.
ways associated with holosystolic MR that was central and directed either centrally or toward the posterior commissure. No obvious apical leaflet tethering was observed, and the coaptation point did not appear to be apically displaced. Marked LV and annular dilatation and very pronounced global LV hypokinesia were obvious.

Leaflet Dynamics

Leaflet dynamics were derived from the 5 animals having both leaflet edge markers (No. 35 and 36, Figure 1B) remaining in place after rapid pacing. Leaflet edge separation throughout the cardiac cycle is shown in Figure 4. The time of valve closure (defined as the time at which leaflet edge separation reached its minimum plateau), as timed from ED, was not significantly different before and after TIC (70±18 versus 87±14 ms, P=0.23). Systolic leaflet separation distance, however, increased (5.2±0.9 versus 6.8±1.2 mm, P=0.019), indicating decreased leaflet coaptation. Leaflet edge separation distance after valve closure before and after cardiomyopathy and degree of MR for these 5 animals are shown in Table 3. A positive correlation (Spearman’s ρ = 0.89) was observed between the change in leaflet separation distance and degree of MR. Leaflet geometry shortly after valve closure (100 ms from ED) before and after development of cardiomyopathy is shown in Figure 5. Significant septal-lateral annular dilatation occurred, but mitral leaflet shape was unchanged. When baseline conditions were compared with TIC, angular displacement for the anterior leaflet edge (Θ35, Figure 6) shortly after (100 ms from ED) valve closure (29.2±4.5° versus 26.7±3.2°, P=0.3) and at end systole (29.7±6.4° versus 26.3±2.8°, P=0.3) did not change. Similarly, the posterior leaflet edge angular displacement (Θ36, Figure 6) was unaffected at 100 ms from ED (54.8±14.6° versus 44.2±10.7°, P=0.13) and at end systole (53.3±13.6° versus 40.2±8.1°, P=0.07). To further confirm the absence of apical leaflet edge displacement with TIC, the distance at end systole from the annular plane (best-fit plane to the annular markers) to each leaflet edge marker was calculated before and after the development of cardiomyopathy. The distance to the annular plane actually decreased, but the decrement did not reach statistical significance for both the anterior (7.7±3.2 versus 5.0±3.3 mm, P=0.16) and posterior (7.8±7.7 versus 5.7±4.0 mm, P=0.15) leaflet edges with TIC. Thus, pacing did not alter leaflet position relative to the mitral annulus shortly after valve closure and at end systole.

Discussion

Dilated cardiomyopathy is often complicated by functional MR, but the exact mechanisms responsible for this MR continue to be debated. Using an ovine model of TIC, we found significant systolic-annular dilatation occurred, but mitral leaflet shape was unchanged. When baseline conditions were compared with TIC, angular displacement for the anterior leaflet edge (Θ35, Figure 6) shortly after (100 ms from ED) valve closure (29.2±4.5° versus 26.7±3.2°, P=0.3) and at end systole (29.7±6.4° versus 26.3±2.8°, P=0.3) did not change. Similarly, the posterior leaflet edge angular displacement (Θ36, Figure 6) was unaffected at 100 ms from ED (54.8±14.6° versus 44.2±10.7°, P=0.13) and at end systole (53.3±13.6° versus 40.2±8.1°, P=0.07). To further confirm the absence of apical leaflet edge displacement with TIC, the distance at end systole from the annular plane (best-fit plane to the annular markers) to each leaflet edge marker was calculated before and after the development of cardiomyopathy. The distance to the annular plane actually decreased, but the decrement did not reach statistical significance for both the anterior (7.7±3.2 versus 5.0±3.3 mm, P=0.16) and posterior (7.8±7.7 versus 5.7±4.0 mm, P=0.15) leaflet edges with TIC. Thus, pacing did not alter leaflet position relative to the mitral annulus shortly after valve closure and at end systole.

![Figure 3](image-url)  
**Figure 3.** Three-dimensional reconstruction of mitral annulus at end systole during baseline (●, solid line) and after development of dilated cardiomyopathy (TIC, ○, dashed line). No. 22 is mid-septal (“saddlehorn”) annular marker; No. 18, midlateral annular marker. ACOM indicates anterior commissure; PCOM, posterior commissure.

![Figure 4](image-url)  
**Figure 4.** Leaflet edge separation (cm) at baseline (●) and after development of TIC (○). A 700-ms time window centered at ED (t=0) is illustrated. Error bars indicate 1 SEM.

![Figure 5](image-url)  
**Figure 5.** Leaflet shape (derived from 3D coordinates of leaflet markers) looking roughly from anterior commissure toward posterior commissure after valve closure (6 frames [100 ms] after ED) for baseline (●) and TIC (○). Error bars indicate 1 SEM.

**TABLE 3. Leaflet Edge Separation**

<table>
<thead>
<tr>
<th>Animal</th>
<th>Baseline, mm</th>
<th>TIC, mm</th>
<th>Change, mm</th>
<th>MR+</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6.2</td>
<td>8.2</td>
<td>2.0</td>
<td>2.5</td>
</tr>
<tr>
<td>2</td>
<td>5.7</td>
<td>6.2</td>
<td>0.5</td>
<td>1.5</td>
</tr>
<tr>
<td>3</td>
<td>5.0</td>
<td>5.8</td>
<td>0.8</td>
<td>1.5</td>
</tr>
<tr>
<td>4</td>
<td>5.1</td>
<td>7.9</td>
<td>2.8</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>4.0</td>
<td>5.8</td>
<td>1.8</td>
<td>1.5</td>
</tr>
</tbody>
</table>

Mean systolic leaflet edge separation distance after mitral valve closure.
increase in mitral annular area and mitral septal-lateral annular diameter. These changes were associated with impaired mitral leaflet coaptation and development of significant MR but without alteration of the systolic position of the mitral leaflets relative to the annulus. Thus, our study indicates that incomplete mitral leaflet coaptation arising from annular dilatation is primarily responsible for the pathogenesis of MR in pacing-induced cardiomyopathy.

**LV Geometry**

LV chamber dilatation and reduced systolic function are the hallmarks of end-stage cardiomyopathy, both clinically and in experimental models. The cardiomyopathic conditions in this study were associated with a significant increase in LV chamber size and more spherical LV chamber shape, as described by others. LV end-diastolic pressure and end-systolic volume increased reflecting LV systolic dysfunction. Pacing cardiomyopathy has also been associated with LV wall thinning, confirmed in our model. Indeed, the myocardial thinning was quite symmetrical in that the anterior, lateral, and posterior LV walls all showed significant reduction in wall thickness. Thus, rapid pacing in sheep produced changes in LV shape, size, and systolic function consistent with the published literature and emulated the clinical dilated cardiomyopathy state.

**Pathogenesis of MR**

TIC was associated with significant MR in the present study. Functional MR has been reported in experimental end-stage cardiomyopathy and ascribed to increased LV chamber sphericity, which displaces the papillary muscles with resultant systolic leaflet tethering as evidenced by an increase in the perpendicular distance between the mitral annular plane and coaptation region of the mitral leaflets. In an acute model of LV dilatation, Otsuji and coworkers confirmed the importance of altered LV geometry and papillary muscle position in producing MR. Displacement of the coaptation zone away from the annular plane, as assessed by transesophageal echocardiography, has also been reported in patients with dilated cardiomyopathy. MR in that study, however, also was correlated with annular dilatation. Although greater LV chamber sphericity and size were observed in our study, the geometric relationship of the mitral leaflets to the mitral annulus, as evidenced by the angular displacements of leaflet edge markers and leaflet edge distance to the annular plane, did not change with the development of cardiomyopathy, and leaflet shape shortly after valve closure was also unchanged. Perhaps these differences are attributable to different experimental models (eg, tachycardia versus ischemia, interspecies differences). In any event, apical displacement of the leaflet coaptation point secondary to LV shape change was not the cause of MR in our study; as always, this could represent a type II (or B) statistical error that occurs when only a small number of animals are available for analysis.

An insufficient degree of mitral leaflet coaptation, however, was demonstrated in the present investigation because the systolic separation of leaflet edges increased after the development of TIC. The change in leaflet edge separation after mitral valve closure between baseline and TIC correlated with the degree of MR (Table 3). Although the level of coaptation, as delineated by the position of leaflet edge markers, was unaltered relative to the mitral annulus, the leaflets were farther apart during systole after the development of cardiomyopathy. Therefore, MR in TIC was associated with Carpentier type I leaflet motion (normal) rather than type IIb restricted systolic leaflet motion. These findings imply that leaflet annular hinge point separation and annular dilatation were responsible for the larger leaflet separation distance, resulting in MR. This is in accord with the clinical observations of Boltwood and colleagues, who reported that annular size was the chief determinant of valve incompetence in patients with dilated cardiomyopathy. Furthermore, no difference in chordal length, angulation, or tethering length was observed in cardiomyopathic patients with and without MR. At end systole, mitral annular area in our study increased by 46 ± 13% while the septal-lateral annular diameter dilated by 29 ± 10%, confirming a substantial degree of annular enlargement in end-stage cardiomyopathy. This degree of annular dilatation alone could be responsible for mitral incompetence because an isolated 25% increase in mitral annular circumference, attained with an externally adjustable, rigid mitral ring in an otherwise normal heart, has been shown to result in moderate to severe MR in vivo. Furthermore, in a finite element analysis by Kunzelman and associates, an 18% increase in annular circumference was associated with incomplete coaptation throughout systole without displacement of the coaptation point.

Some clinical and experimental data speak against annular dilatation as the primary cause of functional MR in cardiomyopathy. Human mitral valve leaflet surface area is 1.5 to 2.2 times the area of the mitral annulus, and this natural redundancy of leaflet tissue is thought to blunt the effect that annular dilatation may have on the pathogenesis of functional MR. Leaflet coaptation occurs below the annular...
plane (toward the LV apex), however, and leaflet redundancy relative to the annular septal-lateral diameter is effectively decreased. It follows that significant annular septal-lateral dilatation, such as that seen in our study, could exhaust this redundancy and result in incomplete leaflet coaptation and MR. In sheep, the leaflet area is only 52% greater than the annular area,26 and the end-systolic 46% increase in annular area seen in this study could certainly account for the observed increase in mitral leaflet edge separation with the consequent MR. Although subvalvular remodeling cannot be excluded as a mechanism, the clinical efficacy of an undersized complete27 or partial ring annuloplasty6 alone in correcting MR in patients with dilated cardiomyopathy further suggests that annular dilatation may be the primary cause of functional MR. Because septal-lateral annular dilatation appears to be particularly important to the pathogenesis of MR in cardiomyopathy, surgical approaches to valve repair in dilated cardiomyopathy should specifically aim to reduce and fix this dimension. This may be best achieved by using a rigid, complete annuloplasty ring that exerts more narrowing stresses in the annular septal-lateral dimension than flexible or partial ring annuloplasty.

Conclusions
MR in this ovine model of TIC was primarily the result of mitral annular dilatation and separation of the leaflet hinge points, which led to incomplete leaflet coaptation and valve incompetence. Altered subvalvular leaflet tethering did not appear to play a major role in the pathogenesis of MR in this model. These findings support the clinical application of annular reduction procedures, such as annuloplasty with a rigid, complete ring, to correct functional MR in patients with dilated cardiomyopathy.

Study Limitations
Important limitations of this study must be noted before the data are interpreted in a clinical context. The average degree of MR observed in our study was moderate, which is less than the moderate to severe or severe MR observed clinically in patients with dilated cardiomyopathy. Because only 5 animals had both leaflet edge markers to assess changes in the location of the coaptation zone and only 1 of these animals had severe MR, it is possible that if more animals with severe MR were studied, apical displacement of leaflet edges with TIC would have been demonstrated. Despite this possibility, we did not observe apical displacement of the coaptation zone in the 1 animal with severe MR. Furthermore, we analyzed leaflet edge position only at the center of each leaflet, because no other leaflet edge markers were implanted along the line of coaptation. Thus, no data are available on leaflet position near the commissures. The MR in most animals was central; therefore, leaflet edge position data at the center of the valve are most relevant. The MR in ovine TIC may not be representative of functional MR in humans because of interspecies differences in cardiac anatomy. Leaflet occlusion area relative to the mitral orifice is smaller in sheep than in humans25,26; although annular dilatation may exhaust this maximal coaptation area in an ovine heart, this may not be true in human hearts. Sheep have a less well-defined posterior annulus than humans and more atrial tissue above and below the line of leaflet insertion,29 but mitral annular dynamics are similar in both sheep18 and human hearts.30 Moreover, rapid-pace cardiomyopathy exhibits the hemodynamic16,17 and neurohumoral30 changes seen in human heart failure and is considered a good model of the clinical entity. The myocardial marker method provides reproducible determination of 3D marker position with submillimeter spatial resolution every 16.7 ms but requires suturing small metal markers to intracardiac structures. It is unlikely that the markers interfered with mitral leaflet motion because they are very small (aggregate mass, 20±6 mg). Even when we grossly overloaded the anterior leaflet with a larger number of excessively heavy markers (total mass, 184 mg) in another experiment, the peak anterior leaflet opening velocity by epicardial pulsed-wave Doppler echo was 0.47±0.05 compared with 0.45±0.06 m/s for leaflets without any markers implanted. The peak E-wave velocities ranged from 0.55 to 0.60 m/s (unpublished data). Thus, the markers per se do not alter normal leaflet dynamics.

Acknowledgments
This work was supported by grant HL-29589 from the National Heart, Lung and Blood Institute. Drs Timek, Lai, and Dagum are Carl and Leah McConnell Cardiovascular Surgical Research Fellows. Dr Timek is also a recipient of the Thoracic Surgery Foundation Research Fellowship Award. Dr Dagum was also supported by NHLBI INRSA HL-0956. Dr Lai was supported by a fellowship from the American Heart Association, Western States Affiliate. We appreciate the superb technical assistance provided by Mary K. Zasio, BA, Carol W. Mead, BA, Erin M. Schultz, BS, and Maggie Brophy. We also thank Medtronic, Inc for the loan of the rapid-pacing pulse generator and donation of the epicardial pacing leads.

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doi: 10.1161/hc37t1.094913
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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