Changes in Diastolic Function During Development and Correction of Chronic LV Volume Overload Produced by Mitral Regurgitation

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Background. Mitral regurgitation (MR) causes an augmentation in left ventricular (LV) diastolic function, increasing early diastolic filling rate and decreasing LV stiffness. Whether these changes in diastolic function persist, return to normal, or become abnormal after mitral valve replacement (MVR) is unknown.

Methods and Results. Simultaneous LV echocardiography and catheterization studies were performed in six dogs in the baseline state (baseline), 3 months after creation of MR (chronic MR), and 3 months after MVR. Chronic MR caused LV dilation (end-diastolic dimension increased from 4.5±0.1 cm in baseline to 5.8±0.1 cm in chronic MR, p<0.05) and eccentric LV hypertrophy (LV-to-body weight ratio increased from 3.6±0.2 g/kg in baseline to 4.9±0.4 g/kg in chronic MR, p<0.05). Chronic MR caused an increase in LV early diastolic filling rate (peak rate of increase in minor-axis dimension increased from 11±1 cm/sec in baseline to 18±1 cm/sec in chronic MR, p<0.05), did not change the time constant of myocardial relaxation (τ was 31±4 msec in baseline and 30±2 msec in chronic MR), and caused a decrease in the modulus of regional chamber stiffness from 7.7±1.2 in baseline to 2.4±0.03 in chronic MR, p<0.05. MVR caused the resolution of LV dilation (end-diastolic dimension returned to normal [4.8±0.2 cm]), but three months after MVR, regression of LV hypertrophy was incomplete (LV-to-body weight ratio remained elevated [4.4±0.5 g/kg]). After MVR, LV early diastolic filling rate (8±1 cm/sec), the relaxation time constant (31±2 msec), chamber stiffness (7.1±1.8), myocardial stiffness (11.2±3.1), and LV end-diastolic pressure (8±1 mm Hg) returned to normal.

Conclusions. The enhanced diastolic function seen in chronic MR returned to normal after correction of the chronic volume overload by MVR. (Circulation 1993;87:1378–1388)

Key Words • relaxation • left ventricle • valves

Patients with mitral regurgitation (MR) may remain compensated, without symptoms of congestive heart failure, for many years. To remain compensated, however, the left ventricle must dilate, increase stroke volume, and maintain acceptable left ventricular (LV) diastolic pressures. Recent studies have demonstrated that these compensatory changes depend, at least in part, on changes in LV diastolic function.1–3 Chronic MR causes an increase in the rate and extent of LV early diastolic filling. Chronic MR also causes a decrease in LV chamber stiffness (as indicated by a decline in steepness and rightward shift of the diastolic LV pressure–versus–dimension relation). These changes allowed the left ventricle to dilate with only a limited increase in LV end-diastolic and mean pulmonary capillary wedge pressure.

Mitral valve replacement (MVR) has been shown to be effective in correcting the volume overload caused by chronic MR.6 Clinical and experimental studies have defined the effects of MVR on operative mortality, long-term survival rates, clinical symptoms, LV volume, LV mass, and LV systolic function.7–29 However, no studies have been performed to examine the effects of MVR on LV diastolic function. Specifically, it is unknown whether the compensatory changes in diastolic function are reversible after the volume overload has been corrected. In aortic valve disease, aortic valve replacement has been shown to cause an increase in myocardial stiffness in some patients.30 In addition, even when LV systolic function is normal after aortic valve replacement, abnormalities in LV diastolic function may cause abnormal exercise hemodynamics.31 Thus, postoperative changes in diastolic function may play an important role in determining the hemodynamic response to the postoperative remodeling caused by the reduction in LV volume, the regression of LV hypertrophy, and the fall in systolic ejection fraction that usually

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accompanied MVR. Therefore, the purpose of the present study was to define the effect of MVR on LV diastolic function in dogs with chronic MR (in particular, the rate of LV isovolumic pressure decline, the rate of early diastolic filling, and LV stiffness) and to test the hypothesis that when the LV volume overload is corrected, diastolic function returns to normal.

Methods
Simultaneous echocardiography and catheterization were used to examine serial changes in indexes of LV volume, mass, and diastolic function in six dogs during the progression and regression of volume overload. Changes in systolic function in these dogs have been summarized in a previous study. In the present study, dogs were studied in the baseline state (baseline data), 3 months after the creation of MR (chronic MR data), and 3 months after MVR (MVR data). Because the study was longitudinal, each animal served as its own control. The baseline and the chronic MR data from two dogs were included in a previous study; the MVR data from these two dogs have not been published; data from all three states in four additional dogs have not been published.

Creation of MR
MR was produced by a technique previously described in detail. Briefly, a urologic calculus-retrieving forceps was introduced into the left ventricle through a sheath and was used to grasp chordae tendineae. Forceful retraction of the grasping forceps disrupted the chordae tendineae, producing MR. Severe MR was indicated by a fall in forward stroke volume by 50% and/or a rise in pulmonary capillary wedge pressure to 20 mm Hg. Thermodilution cardiac output determination and ventriculography were performed to confirm the severity of MR and to calculate regurgitant fraction. The amount of MR produced in the dogs discussed in this study was comparable to our previous studies; regurgitant fraction for dogs included in this study was 65±5%.

MVR
Anesthesia was induced with intramuscular injection of droperidol/fentanyl (0.15 mL/kg). The animal was tracheally intubated and placed on a mechanical ventilator. Before extracorporeal circulation, anesthesia was maintained by inhalation of 0.5% isoflurane and a constant infusion of sufentanil (0.2 g·kg⁻¹·min⁻¹). A radial artery cannula was inserted to monitor arterial blood pressure, and a central venous catheter was inserted for an infusion of drugs and for the measurement of central venous pressure. A left thoracotomy was performed. After pericardiotomy, the heart was suspended in a pericardial cradle. The right atrium and right femoral artery were cannulated, and the cannulas were connected to extracorporeal circulation in the standard fashion. After the aorta was cross-clamped, cardioplegia was induced by intracoronary infusion of cold hyperkalemic cardioplegic solution. The animal was cooled to 28°C. MVR was performed via a left atriotomy with a 21-, 23-, or 25-mm pericardial xenograft prosthesis (Ionescue-Shiley, Inc., Irvine, Calif.). The chordae tendineae were severed. The valve was sewn to the mitral annulus with a continuous suture. The average cross-clamp time was 32±4 minutes. After removal of the cross-clamp, air was evacuated and the left atriotomy was closed. Defibrillation was performed with internal paddles and discharge of 10–15 J. The animal was warmed to 35°C and separated from extracorporeal circulation, and the thoracotomy and femoral vessels were repaired. Anesthesia after surgery was maintained with an intravenous infusion of sufentanil (0.2 g·kg⁻¹·min⁻¹), which was gradually decreased over a period of 12 hours and supplemented with acepromazine. Over the next 24 hours, the animal underwent constant supervision by one of the authors (Dr. Zile, Carabello, Ishihara, or Nakano). Arterial blood gas determinations and electrolytes were obtained hourly and corrected as necessary. Twenty-four hours after surgery, all animals could be extubated, and all intra-arterial and intravenous cannulas were removed. The animal was then followed longitudinally for 3 months. During this period of time, Doppler echocardiographic examinations were performed to look for the development of prosthetic MR. One of the six animals developed MR 1.5 months after surgery and was therefore excluded from the study.

Simultaneous LV Echocardiography and Catheterization
The animal was sedated with droperidol/fentanyl (0.15 mL/kg i.m.). Under sterile technique and 2% xylocaine anesthesia, an incision was made over the cervical vessels to expose and isolate the carotid artery and jugular vein. A thermodilution Swan-Ganz catheter was advanced to the pulmonary capillary wedge position under fluoroscopic and hemodynamic guidance. A 7F double micromanometer–tipped catheter (PC780, Millar Instruments, Houston, Tex.) was externally calibrated to mercury at 37°C and advanced to the LV under fluoroscopic guidance. The distal micromanometer was positioned in the LV, and the proximal micromanometer was placed in the proximal aorta. The calibration for both micromanometers was confirmed and matched to a 5F fluid-filled pigtail catheter connected to a transducer (Statham P23dB, Oxnard, Calif.) placed at the midchested level. LV, aortic, and pulmonary capillary wedge pressures were recorded simultaneously with LV echocardiography at a paper speed of 100 mm/sec.

Two-dimensional, M-mode, and Doppler echocardiographic studies (ATL Ultramark VI, 2.25-MHz and 3.5-MHz transducers, Bothell, Wash.) were performed from the right parasternal and apical areas. Short-axis and long-axis views were obtained in all dogs. These methods have been described previously in detail.

Echocardiographic data were measured according to the American Society of Echocardiography criteria, including the leading edge convention. End diastole was defined at the Q wave of the ECG. End systole was defined at the peak downward motion of the interventricular septum (end ejection). In normal subjects, this corresponds to the aortic diastolic notch and the second heart sound (aortic valve closure). We recognize that this relation may not be constant in subjects with mitral regurgitation. In the present study (as in our previous study), however, end-ejection measurements were used because they were easily defined and reproducible. Left
atrial dimension was measured from the long-axis view according to the method described by Reed et al.\textsuperscript{1380} LV pressure and echocardiograms were processed by a semiautomated technique similar to that used in previous studies.\textsuperscript{5,33} Pressure and M-mode echocardiographic records were placed on a digitizing table (Summasketch, Summagraphics, Fairfield, Conn.) and manually traced with a cursor. The position of the cursor was detected and converted to digital coordinates for processing by a microcomputer system (NCR PC8, Akron, Ohio). LV pressure, minor-axis dimension, and wall thickness were digitized with a sampling interval of 5 msec. Data were smoothed with a seven-point, third-order, least-squares orthogonal polynomial fit. The derivatives of pressure, dimension, and thickness with respect to time were obtained from the smoothed data. Typical examples of plots of dimension and thickness versus time are shown in Figures 1 and 2 for baseline, chronic MR, and MVR.

**Calculations**

LV mass was calculated by the recently validated formula of Feneley et al\textsuperscript{1380}: LV mass equals echocardiographic cross-sectional area (CSA) times long-axis dimension. In our laboratory, there has been a good correlation between echocardiography-derived LV mass, angiography-derived LV mass, and mass measured at autopsy.\textsuperscript{5,33} Fractional shortening and circumferential global average wall stress (assuming a cylindrical or spherical geometry) were calculated from previously published formulas.\textsuperscript{5,33} Values of stress measured at end diastole, peak systole, end systole, and mitral valve opening are presented in Table 1.

**Diastolic function.** The time constant of isovolumic pressure decline ($\tau$) was calculated from time-expanded recordings of LV pressure digitized at 5-msec intervals beginning at peak ($-\Delta$)$dP/dt$ and ending at mitral valve opening by three different methods ($\tau_a$, $\tau_m$, and $\tau_n$). The formulas used to calculate each of these measurements of the time constant have been published previously.\textsuperscript{5,33} Agreement between the three methods will support the reproducibility of the results. $\tau_a$ was calculated by the original method described by Weiss et al\textsuperscript{137} with the assumption that $P_B$ (the baseline pressure toward which the monoexponential decays) equals zero. It is recognized, however, that $P_B$ may not be zero in this preparation. Therefore, we also used a three-constant, nonlinear regression method described by Mirsky\textsuperscript{138} to calculate $\tau_m$. It is also recognized that in the presence of MR, LV pressure decline from peak ($-\Delta$)$dP/dt$ to mitral valve opening may not be totally isovolumic. The amount of LV volume ejected into the left atrium after aortic valve closure is probably quite small and should not significantly affect this analysis. However, in addition to examining $\tau_a$ and $\tau_m$ (indexes of ventricular relaxation), $\tau_n$ (an index of myocardial relaxation) was also examined. This index of myocardial relaxation was first used by Pouleur et al\textsuperscript{139} in patients with coronary artery disease. Its use has been reviewed by Mirsky et al\textsuperscript{138} and it has been proposed for use in mitral and
The left atrial-to-LV transmitral pressure gradient was not measured directly. Rather, the difference between the pulmonary capillary wedge pressure at the peak of the V wave (PCWP_v) and the LV minimum pressure (LVP_min) was used as an index of the early diastolic transmitral pressure gradient. The PCWP_v was chosen because it occurs at or near the time of mitral valve opening (i.e., the time at which LV pressure falls to a value equal to the peak of the V wave in the pulmonary capillary wedge pressure). In so doing, we took into account the delay between pressure transients measured by the pulmonary capillary wedge catheter and those measured in the left atrium. This method, therefore, did not allow measurement of instantaneous transmitral gradients throughout filling but did provide an index of the maximum early diastolic transmitral pressure gradient at mitral valve opening.

Regional chamber stiffness constant (K_c) and regional myocardial stiffness constant (K_m) were calculated from
LV echocardiographic and catheterization data. The calculation of chamber and myocardial stiffness constants was based on the analysis of the curvilinear diastolic pressure–volume and stress–strain relations. Methods used to apply these concepts to the pressure–dimension–thickness data used in this study were developed by Mirsky.38

LV chamber stiffness was quantified by examining the relation between LV pressure and dimension measured from the end of the early rapid filling period to end diastole. These data were fit by an exponential equation:

$$P = A e^{k_c (\pi D^2/4\text{CSA})}$$  \hspace{1cm} (1)

where the relation between $dP/d(\pi D^2/4\text{CSA})$ and $P$ is linear and the exponent $k_c$ (the slope of this linear relation) is the modulus of LV chamber stiffness. This equation was derived (for use with echocardiographic data) from standard techniques (used with angiographic data) in which diastolic pressure and volume were fit by an exponential equation:

$$P = A e^{\beta(V/V_w)}$$  \hspace{1cm} (2)

where the relation between $dP/d(V/V_w)$ and $P$ is linear and the exponent $\beta$ (the slope of this linear relation) is the modulus of LV chamber stiffness. In the present study, the left ventricle was modeled as a cylindrical annulus; the volume of a cylinder,  

$$V = \pi D^2 L/4$$  \hspace{1cm} (3)

was substituted for $V$ in Equation 2; wall volume of a cylinder,  

$$V_w = \text{CSA} \times L$$  \hspace{1cm} (4)

was substituted for $V_w$ in Equation 2. By use of these methods, a modulus of regional chamber stiffness ($k_r$) was calculated from echocardiographically determined dimension data. By fitting all the coordinates of pressure versus dimension measured from the end of the early filling period to end diastole by Equation 1, $k_r$ becomes a single numerical value that represents the entire P-versus-$\pi D^2/4\text{CSA}$ curve. $k_r$ generally reflects the shape or steepness of the curvilinear P-versus-$\pi D^2/4\text{CSA}$ relation but does not reflect this relation’s position along the abscissa. Therefore, a graphic method to show the average P-versus-$\pi D^2/4\text{CSA}$ relation for all six dogs in each of the three states was used. Since the P-versus-$\pi D^2/4\text{CSA}$ relation in each dog, when multiple coordinates were used throughout diastole, was well fit by an exponential function, the mean±SEM of values for the P-versus-$\pi D^2/4\text{CSA}$ coordinates were summarized for all six dogs at only two points during diastole; i.e., at minimum LV diastolic pressure and at end-diastolic pressure. These two points were then plotted assuming an exponential (or at least a curvilinear) relation between the coordinates. This graphic presentation allowed us to summarize data from all six dogs and show the slope and position of P versus $\pi D^2/4\text{CSA}$. Thus, the effects of chronic MR and MVR on chamber stiffness were displayed in three ways: 1) a representative example of the P-versus-$\pi D^2/4\text{CSA}$ relation using all diastolic data from the end of rapid filling to end diastole (Figure 3); 2) the mean±SEM value of the modulus of chamber stiffness, $k_r$, calculated on the basis of all the diastolic data from the end of the early filling period to end diastole (Table 2); and 3) a graphic summary of the P-versus-$\pi D^2/4\text{CSA}$ relation from all dogs taken from two points during diastole (Figure 4).

Myocardial stiffness was quantified by examining the relation between LV wall stress and dimension measured from the end of the early rapid filling period to end diastole. These data were fit by the power function

$$\sigma = AD^\delta$$  \hspace{1cm} (5)

where the relation between $d\sigma/dD$ and $\sigma$ is linear and the exponent $k_m$ (the slope of this linear relation) is the modulus of myocardial stiffness. This formula was derived (for use with echocardiographic data) from standard techniques (used with angiographic data) in which diastolic stress and strain were fit by the power function

$$\sigma = A \epsilon^\delta$$  \hspace{1cm} (6)
TABLE 2. Effect of Mitral Valve Replacement on Diastolic Function

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Chronic MR</th>
<th>MVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV pressure decline (mm Hg/sec)</td>
<td>1,910±150</td>
<td>1,602±212</td>
<td>1,878±163</td>
</tr>
<tr>
<td>τa (msec)</td>
<td>31±1</td>
<td>30±2*</td>
<td>31±2</td>
</tr>
<tr>
<td>τr (msec)</td>
<td>33±1</td>
<td>32±4*</td>
<td>34±2</td>
</tr>
<tr>
<td>τw (msec)</td>
<td>33±2</td>
<td>33±2</td>
<td>31±2</td>
</tr>
<tr>
<td>LV diastolic filling</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(+)dD/dt (cm/sec)</td>
<td>11±1</td>
<td>18±1</td>
<td>8±1‡</td>
</tr>
<tr>
<td>(+)D · dt⁻¹ · D⁻¹ (seconds⁻¹)</td>
<td>2.7±0.2</td>
<td>4.0±0.1†</td>
<td>2.1±0.2‡</td>
</tr>
<tr>
<td>(−)dD/dt (cm/sec)</td>
<td>3.5±0.1</td>
<td>5.5±0.4†</td>
<td>3.0±0.3‡</td>
</tr>
<tr>
<td>(−)dD · dt⁻¹ · th⁻¹ (seconds⁻¹)</td>
<td>2.6±0.1</td>
<td>4.6±0.4†</td>
<td>2.5±0.3‡</td>
</tr>
<tr>
<td>Stiffness constant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kc</td>
<td>7.7±1.2</td>
<td>2.4±0.3†</td>
<td>7.1±1.8‡</td>
</tr>
<tr>
<td>Km</td>
<td>9.6±1.8</td>
<td>9.8±3.4</td>
<td>11.2±3.1</td>
</tr>
</tbody>
</table>

MR, mitral regurgitation; MVR, mitral valve replacement; τa, time constant using Weiss et al; τr, time constant using Mirsky method; τw, myocardial relaxation rate; (+)dD/dt, peak rate of increase in minor-axis dimension; (−)dD/dt, peak wall thinning rate; τw, chamber stiffness constant; Km, myocardial stiffness constant.

*Note limitations section of discussion.
†p<0.05 vs. baseline; ‡p<0.05 vs. chronic MR.

where the relation between dσ/dε and σ is linear and δ is the modulus of myocardial stiffness. In the present study, myocardial stiffness was calculated as incremental endocardial strain based on minor-axis dimension measurements, and the exponent km was multiplied by a geometric factor (which for a cylinder is 3/4). With these methods, a modulus of regional myocardial stiffness (km) was calculated from echocardiographically determined dimension and wall thickness data by the equation

$$K_m = \frac{Dd\sigma}{dD}$$

(7)

The effects of chronic MR and MVR on myocardial stiffness were displayed by methods similar to those used to quantify chamber stiffness (described above). That is, all the coordinates of the LV diastolic stress–versus–dimension relation from the end of early rapid filling to end diastole were used to calculate the modulus of myocardial stiffness (km) (Table 2) and to generate the representative examples shown in Figure 3. The average stress–versus–dimension relation for each dog was presented in graphic summary form using coordinates of stress versus dimension measured at two points in diastole, minimum pressure, and end diastole (Figure 5).

Statistical Analysis

Data are presented as mean±SEM. Because of the small number of observations made at each time period, the nonparametric Friedman's two-way ANOVA was used to find differences between groups. If a difference was found, a Wilcoxon rank order test was then applied to determine where the differences existed.

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 the Care and Use of Laboratory Animals prepared by the National Academy of Sciences and published by the National Institutes of Health (NIH publication #85-23, revised 1985).
Results

LV Volume and Mass

Chronic MR caused LV dilation (end-diastolic dimension increased from 4.5±0.1 cm in baseline to 5.8±0.1 cm in chronic MR, p<0.05) and the development of modest LV hypertrophy (LV-to-body weight ratio increased from 3.6±0.2 g/kg in baseline to 4.9±0.4 g/kg in chronic MR, p<0.05). Chronic MR caused an increase in fractional shortening and total stroke volume (stroke dimension was increased from 1.4±0.1 cm in control animals to 2.3±0.1 cm in chronic MR, p<0.05). (See Table 1.)

MVR caused a reduction in LV enlargement (end-diastolic dimension returned toward baseline and was 4.8±0.2 cm after MVR). MVR caused a small reduction in LV mass, but the regression of LV hypertrophy was incomplete (LV/body weight ratio fell to 4.4±0.5 g/kg after MVR but did not approach the baseline value). MVR caused a significant reduction in fractional shortening to 24±1% (p<0.05 versus baseline and chronic MR), but total stroke volume returned to baseline (stroke dimension was 1.2±0.1 cm after MVR).

LV Pressure and Wall Stress

Chronic MR caused reductions in LV peak and end-systolic pressures but caused increases in LV end-diastolic pressure, mitral valve opening pressure, and pulmonary wedge pressures compared with baseline. Peak systolic stress was unchanged compared with baseline. End-systolic wall stress fell from 176±6 g/cm² in the baseline state to 143±9 g/cm² in chronic MR. End-diastolic and mitral valve opening stress were markedly increased compared with baseline.

MVR caused LV peak and end-systolic pressures, LV end-diastolic pressure, mitral valve opening pressure, and pulmonary wedge pressure to return to baseline. MVR caused a small increase in peak systolic stress, but end-systolic stress rose significantly to 231±11 g/cm² (p<0.05 versus chronic MR and baseline). End-diastolic and mitral valve opening stresses returned to baseline. (See Tables 2 and 3.)

LV Diastolic Function

See Table 2 and Figures 1–5. Chronic MR caused an increase in the rate of early diastolic filling (peak [+]dD/dt increased from 11±1 cm/sec in baseline to 18±1 cm/sec in chronic MR and peak [-]dD/dt increased from 3.5±1 cm/sec in baseline to 5.5±1 cm/sec in chronic MR, both p<0.05). Chronic MR did not significantly alter \( \tau_s \) or \( \tau_e \) compared with baseline. Chronic MR increased the transmitral pressure gradient from 6±1 mm Hg in baseline to 19±4 mm Hg in chronic MR (p<0.05) and increased LV wall stress at mitral valve opening from 12±2 g/cm² in baseline to 37±6 g/cm² in chronic MR (p<0.05). Chronic MR caused a significant decrease in the chamber stiffness constant (k, fell from 7.7±1.2 in baseline to 2.4±0.3 in chronic MR, p<0.05) but did not change the myocardial stiffness constant (k_m was 9.6±1.8 in baseline and 9.8±3.4 in chronic MR).

MVR caused LV early diastolic filling rate to return to normal (peak [+]dD/dt was 8±1 cm/sec; peak [-]dD/dt was 2.1±2.0 cm/sec). The transmitral pressure gradient and LV stress at mitral valve opening returned to normal after MVR (8±1 mm Hg and 21±3 g/cm², respectively). \( \tau_s \) and \( \tau_e \) remained unchanged. The chamber stiffness constant returned to normal (k was 7.1±1.8), and the myocardial stiffness constant remained unchanged (k_m was 11.2±3.1). However, as shown in Figures 3–5, the position of the pressure-versus-dimensional and stress-versus-dimensional curves after MVR remained shifted somewhat to the right of the baseline relation. Although these differences from baseline were not statistically significant, LV dimension was greater for any given stress after MVR than in the baseline state. These differences may reflect the persistent increase in LV mass present 3 months after MVR.

Discussion

A variety of clinical and experimental studies have examined the effects of MVR in subjects with chronic MR. These studies, however, have focused primarily on changes in LV volume, mass, and systolic function. The present study is the first to examine the effects of MVR on LV diastolic function. The present study used a unique model of chronic MR. MR was created in dogs by use of a nonsurgical method to cause chordal rupture. The resultant chronic MR and the consequent changes in LV volume, mass, geometry, and function closely parallel those seen in clinical disease. Changes in diastolic function were assessed in a serial longitudinal fashion; baseline function was compared with changes in function caused by chronic MR and then after MVR in

| Table 3. Hemodynamic Changes Produced by Mitral Valve Replacement |
|-----------------------------|-----------------------------|-----------------------------|
|                            | Baseline | Chronic MR | MVR |
| Heart rate (bpm)           | 74±10    | 74±4        | 62±4 |
| LV mass (g)                | 105±6    | 131±8*      | 121±8* |
| LV/BW (g/kg)               | 3.6±0.2  | 4.9±4       | 4.4±0.5* |
| Catheterization (mm Hg)    |          |             |     |
| LV pressure                |          |             |     |
| Peak systole               | 121±4    | 92±6*       | 119±2† |
| End systole                | 110±4    | 79±5*       | 106±2† |
| Mitral valve opening       | 8±1      | 22±4*       | 9±1† |
| Minimum                    | 2±1      | 3±1         | 1±1  |
| End diastole               | 8±1      | 16±2*       | 8±1† |
| Pulmonary wedge pressure   | 6±1      | 15±2*       | 8±1† |
| PCWPv−LVPmin               | 6±1      | 19±4*       | 8±1† |
| Echocardiography (cm²)     |          |             |     |
| End-diastolic dimension    | 4.5±0.1  | 5.8±0.1*    | 4.8±0.2† |
| End-systolic dimension     | 3.1±0.1  | 3.5±0.1*    | 3.6±0.1* |
| End-diastolic thickness    | 1.0±0.04 | 0.9±0.03    | 1.0±0.05 |
| Fractional shortening      | 33±1     | 40±1*       | 24±1† |
| Stroke dimension           | 1.4±0.1  | 2.3±0.1     | 1.2±0.2† |
| r/th                       | 2.3±0.1  | 3.5±0.1*    | 2.5±0.1† |
| LA/SA                      | 1.5±0.05 | 1.1±0.02*   | 1.5±0.05† |
| Left atrial dimension      | 3.6±0.1  | 5.2±0.2*    | 4.2±0.3† |

* p<0.05 vs. baseline; † p<0.05 vs. chronic MR.
the same animal. The hemodynamic and mechanical measurements made using simultaneous echocardiography and catheterization allowed assessment of changes in both diastolic function itself and many (but not all) of the determinants or mechanisms causing these changes in diastolic function. The present study demonstrated that in this canine model of chronic MR, LV diastolic function returned to normal after MVR. This result was not necessarily predictable. The clinical response in most patients after MVR is complete or nearly complete resolution of symptoms of congestive heart failure.6 These results might predict that LV diastolic function would be normal after MVR. However, the effects of MVR on the known hemodynamic determinants of diastolic function and mechanical determinants of LV function make prediction of the outcome less certain. MVR is associated with a marked fall in ejection fraction, an increase in end-systolic stress, and a fall in left atrial pressure,6 all of which may cause prolongation in the time constant of isovolumic pressure decline and a decrease in early diastolic filling rate. In addition, clinical and experimental studies of MVR demonstrate that LV hypertrophy persists to variable degrees in patients after MVR,8,9,12,19,40 which may cause increased chamber stiffness. The discussion that follows examines the effects of MVR on diastolic function in light of simultaneous changes in hemodynamic and mechanical determinants.

Isovolumic and Filling Indexes of LV Relaxation Rate

In the present study, the effects of MVR on isovolumic relaxation were determined by examining changes in peak (−)dP/dt and the time constant of isovolumic pressure decline. Data from the present study indicate that these indexes of isovolumic relaxation were normal after MVR. The major hemodynamic determinants of isovolumic relaxation include LV end-systolic volume, peak and end-systolic wall stress, and systolic shortening.38,41,42 Data from the present study indicate that after MVR, LV fractional shortening fell but stroke dimension returned to normal; LV end-systolic wall stress increased, but peak stress was normal. These changes in fractional shortening and end-systolic stress would be expected to prolong isovolumic relaxation rate. By contrast, the lack of change in stroke dimension and peak systolic stress would be expected to promote a normal isovolumic rate. It is unclear which of the above factors are preeminent; it is clear, however, that isovolumic relaxation was normal after MVR. Because LV pressure decline is not isovolumic in chronic MR, quantifying the rate of isovolumic pressure decline may be problematic.43 However, correction of chronic MR with MVR should obviate this problem in the postoperative studies. It should be noted that Doppler interrogation of the prosthetic valve in each animal demonstrated normal valve function and no regurgitation.

Changes in LV early diastolic filling rate were determined by examining the peak rate of increase in dimension and the peak wall thinning rate. Data from the present study indicate that these indexes of peak filling rate fell after MVR and returned to normal (baseline) values. The hemodynamic determinants of LV early diastolic peak filling rate include changes in systolic load, but many studies now indicate that the major determinant of peak filling rate is the left atrial—to-left ventricular transmitral pressure gradient.44 Thus, although fractional shortening fell and end-systolic stress increased after MVR, the left atrial–to–left ventricular transmitral gradient returned to normal. These data are concordant, therefore, with other studies, indicating that changes in peak filling rate are determined primarily by changes in the left atrial driving force.

LV Passive Stiffness

Data from the present study indicate that MVR results in a decrease in LV end-diastolic and pulmonary capillary wedge pressures to baseline levels. The major determinants of LV end-diastolic pressure include LV end-diastolic volume and LV chamber stiffness.38,41 In turn, LV chamber stiffness is determined by LV mass, the volume-to-mass (or radius-to-thickness) ratio, and myocardial stiffness.38,41 Data from the present study demonstrate that MVR results in a fall in LV volume to normal and a fall in the volume-to-mass (and dimension-to-thickness) ratios to normal, but there is persistent, mild LV hypertrophy. These data are concordant with previous studies in this laboratory and many other clinical studies. Uniquely, however, the present study demonstrates that MVR causes LV chamber stiffness to increase compared with chronic MR (where stiffness is decreased) and return to a normal baseline value. Thus, change in all of the major determinants of LV passive stiffness (except LV mass) predict that LV stiffness should be normal after MVR. The persistent increase in mass may not cause abnormal stiffness because of its limited extent or its short duration or because it was eccentrically induced. The persistent increase in mass may have caused the stress–versus–dimension relation to remain shifted slightly to the right of baseline after MVR.

Previous Studies Examining Diastolic Function During Regression of Volume Overload

The present study is the first to examine the effect of MVR for chronic MR on LV diastolic function. In addition, there are very few studies that examine the effects of regression of chronic LV volume overload caused by other pathogeneses (such as aortic insufficiency or aortic caval shunt) on diastolic function.30,45–50 The studies by Hess and Krayenbuehl30,48–50 have demonstrated that patients with chronic aortic insufficiency have normal LV chamber stiffness and myocardial stiffness before surgery and that these measurements remain normal after aortic valve replacement. In their studies, chamber and myocardial stiffness remained normal despite persistent ventricular (LV mass) and myocardial (muscle fiber diameter) measurements indicating persistent LV hypertrophy after aortic valve replacement. In addition, these studies demonstrated that LV stiffness remained normal despite an increase in the percent interstitial fibrosis measured by endomyocardial biopsy.

The studies by McCullagh44 and Papadimitriou46 examined the effects of the development of chronic volume overload hypertrophy produced by an aortic caval shunt and the effect of regression of chronic LV volume overload produced by closing the shunt. With the aortic caval shunt open, their study indicated that LV chamber stiffness was increased. By contrast, when the shunt was closed, chamber stiffness returned to normal. As in the studies performed in patients with aortic insufficiency
treated with aortic valve replacement, closure of the shunt was associated with incomplete regression of LV hypertrophy, with LV mass remaining greater than normal. Unlike studies done in aortic insufficiency, studies of the ultrastructural changes in the aortocaval shunt model indicated that the myocardial morphology returned to normal after shunt closure. Therefore, these clinical studies of patients with chronic aortic insufficiency and the experimental studies examining the effect of aortocaval shunt indicate that regression of chronic LV volume overload resulted in normal LV chamber and myocardial stiffness. Data from the present study are concordant with these previous studies.

LV Systolic Function After MVR

Changes in LV diastolic function after MVR were the primary focus of the present study, and changes in LV systolic function were examined in this model in two previous studies.29,32 These studies point out an interesting dissociation between changes in systolic and diastolic function that occur during the development of chronic MR and that follow MVR. Chronic MR causes a clear decrease in LV contractile function (as evidenced by a decrease in maximum systolic elastance and a decrease in peak systolic stiffness); in contrast, chronic MR causes an increase in LV diastolic function (as evidenced by an increase in LV early diastolic filling rate and a decrease in LV chamber stiffness). After MVR, diastolic function decreases toward normal, and contractile function increases toward normal.

A second dissociation between indexes of LV systolic function (contractile state versus ejection performance) is also evident in these studies. During chronic MR, contractile function (maximum elastance, peak systolic stiffness) is decreased, but ejection performance (measured as LV systolic ejection fraction) is normal or increased. This increase in ejection fraction is consequent to a decrease in LV systolic wall stress. After MVR, systolic ejection performance decreases, whereas contractile function increases. This decrease in ejection fraction is consequent to an increase in LV systolic wall stress. These changes in ejection fraction, wall stress, and ejection performance may contribute to the changes seen in LV early diastolic filling rate (as discussed above). After MVR, filling rate decreased, at least in part, because ejection fraction (and thus restoring force) decreased.

Clinical Implications

Data from the present study have important clinical implications. These data suggest that patients with chronic MR and a preserved preoperative ejection fraction will have normal diastolic function after MVR. Data from the present study, however, may not apply to patients with chronic MR and a reduced preoperative ejection fraction. Corin et al4 have demonstrated that LV myocardial stiffness is increased in patients with chronic MR who have a reduced ejection fraction. What effect MVR will have on diastolic function in these patients is unclear. All the animals included in the present study underwent MVR in which both the anterior and posterior chordae tendineae were severed. Therefore, the effect of mitral valve repair or MVR with chordae tendineae left intact on diastolic function cannot be extrapolated from this study. It is likely, however, that diastolic function will remain normal when MR is corrected by these surgical techniques.

Limitations

Quantifying the rate of LV pressure decline in MR using either (−)dP/dt or τ is problematic because LV pressure decline may not be totally isovolumic in the presence of MR. To date, however, there are no studies in chronic MR that have carefully quantified the changes in LV volume that occur between peak (−)dP/dt and mitral valve opening (the time over which LV pressure measurements are made to calculate the relaxation time constant). Two recent studies2,18 suggested that there may be little or no mitral valve flow and little change in LV volume after peak (−)dP/dt. Nonetheless, to compensate for this limitation in examining LV relaxation, an index quantifying myocardial relaxation rate (the time constant of LV wall stress decline) was developed by Pouleur et al39 and Mirsky et al.38 This method recalls the original assumptions intrinsic to the development of the isovolumic time constant. In isolated muscle studies, relaxation rate was assessed by examining the rate of force (or stress) decline. In early studies performed in intact animals, volume and wall thickness (necessary for calculation of wall stress) were not easily measured; LV pressure, however, was routinely available. Since the left ventricle was found to be isovolumic from peak (−)dP/dt to mitral valve opening in normal hearts, changes in wall stress after aortic valve closure were entirely dependent on changes in LV pressure. Therefore, the rate of change of LV pressure was used as a surrogate for LV stress to calculate myocardial relaxation rate. The use of τs simply returns to these original ideas in which τs is a measure of the rate of stress decline and is used as an index of relaxation rate. By using both τs (or τm) and τr, we intended to compensate for the limitation that LV pressure decline may not be totally isovolumic in the presence of MR.

Methods used to calculate LV wall stress were based on assumptions concerning LV geometry. Data from the present study show that the left ventricle became more spherical with chronic MR and returned to a more cylindrical shape (similar to that in baseline) after MVR. Because of this shape change, stress at each study state was calculated for both a spherical and a cylindrical geometry. It was reasoned that if similar directional changes in stress were detected with both geometries, then these differences between study states probably exceeded the differences in stress, which could be caused by a change in geometry alone. Thus, the observed changes in stress probably resulted from the effects of chronic MR and MVR.

Conclusions

Chronic MR resulted in an increase in LV early diastolic filling rate and only a moderate increase in LV end-diastolic pressure. These changes were produced by an increase in left atrial driving force and a decrease in LV diastolic stiffness. The development of volume overload caused by chronic MR resulted in augmented LV diastolic function. These changes in diastolic function were responsible, at least in part, for the ventricle’s ability to compensate for the chronic volume overload.
MVR resulted in normalization of LV early diastolic filling rate and the normalization of LV end-diastolic pressure. These changes were produced by a fall in the left atrial driving force, a fall in LV volume, and normalization of LV diastolic stiffness. The enhancement in diastolic function seen in chronic MR returned to normal after chronic volume overload was corrected by MVR.

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