Role of the Left Atrium in Adaptation of the Heart to Chronic Mitral Regurgitation in Conscious Dogs

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The manner in which the left atrium adapts to chronic mitral regurgitation and the role of the adapted left atrium as a modulator of excessive central blood volume were analyzed in seven conscious dogs, instrumented with high-fidelity pressure transducers and ultrasonic dimension gauges for measurement of left atrial and left ventricular pressure and cavity size. After obtaining data in a control situation, mitral regurgitation was produced by transventricular chordal sectioning. Heart rate was maintained by right atrial pacing, in the "early" stage (7–14 days), left ventricular end-diastolic and mean left atrial pressures increased from 6 to 16 mm Hg and from 4 to 12 mm Hg, respectively. Both left ventricular end-diastolic segment length and left atrial diameter prior to atrial contraction increased by 7%. In the "late" stage (20–35 days), despite significant decreases in left ventricular filling pressure (11 mm Hg) and left atrial pressure (8 mm Hg), there was a continuous increase in left ventricular end-diastolic dimension (10%) and atrial end-diastolic diameter (10%). After the onset of mitral regurgitation, the left atrium performed greater work with a more enlarged cavity. Thus, the enlarged left atrium appears to exert an important compensatory mechanism in the case of excessive central blood volume by buffering pressure rise in the atrium and by providing an adequate ventricular filling volume. (Circulation Research 1988;62:543–553)
were also positioned in the left ventricle and the left atrium for zero pressure reference and for calibration of the micromanometers. A pair of ultrasonic crystals (1.5 mm in diameter, 6.0 MHz) was implanted 1 cm apart into the subendocardial layer of the left ventricle in the minor equator. Another pair of ultrasonic crystals (3.0 mm in diameter, 6.0 MHz) was positioned on the anterior and posterior surfaces of the left atrium for measurement of chamber diameter. A bipolar pacing wire was sutured to the right atrial appendage. A silicone rubber hydraulic cuff occluder (10-16 mm in diameter, IVM, Healdsburg, California) was placed around the inferior vena cava. The pericardium was left open, and all the tubes and wires were exteriorized to the dorsum. After complete recovery from the operation (7-15 days, average 12 days), the control experiment was carried out in conscious dogs lying quietly on the floor.

Subsequently, the dogs were anesthetized and a small thoracotomy was performed at the same area as in the first operation, where the anterior surface of the heart was exposed, and the transmural tissue (average 0.07 gm) was biopsied from the anterior wall of the left atrium. Mitral regurgitation was produced by sectioning the chordae tendinae as described.2 Briefly, a purse-string suture was made in the small avascular area on the anterior wall of the left ventricle, 1 cm below the left circumflex coronary artery and 2 cm lateral to the anterior descending branch. A stab incision was made in the center, and a small hook was inserted to cut the chordae tendinae. When the systolic thrill was noted by palpation on the anterior surface of the left atrium, the wound was closed by tying the purse-string suture. The chest wall was closed in the same manner, and the dogs were allowed to recover. Of the 34 dogs so prepared, five died by acute pulmonary edema; ultrasonic signals were lost in nine during the early stage of the experiment; and 13 had complications of infection, anemia, or malnutrition, and recovery was delayed. Successful serial studies were thus feasible in only seven dogs that recovered rapidly from the second operation and were in good condition at the time of the study. Hemodynamic and dimensional measurements were repeated serially for 3 to 5 weeks in the same manner as in the control study (Figure 1). The data were summarized at two stages after production of mitral regurgitation: at an average of 10 days (range 7-14 days, termed "early" stage) and at an average of 25 days (range 20-35 days, termed "late" stage).

At termination of the study, the dogs were anesthetized, and a transmural biopsy of the anterior wall of the left atrium was repeated. After fixation of the heart, location of crystals was verified. The left atrial crystals were not dislocated in any dog, but the left ventricular subendocardial crystals had moved into the left ventricular cavity in one dog and had been displaced to the subepicardial layer in another dog. Data related to these two crystals were therefore excluded. Finally, heart

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**Figure 1.** Representative tracings serial changes after the production of mitral regurgitation (MR). Recordings at the early stage (10 days after) are shown in the middle and at the late stage (25 days after) on the right. Traces represent, from top to bottom: left ventricular pressure, first derivative of left ventricular pressure (dP/dt), left ventricular segment length, left atrial pressure, left atrial diameter, and bipolar electrocardiogram recorded in the left atrium (ECG).
weight was measured after removal of all the implanted crystals and the pericardium. These values were compared with the normal values estimated by multiplying body weight by 6.6.7

Protocol
In each study, baseline hemodynamic data were obtained at basal resting state during spontaneous sinus rhythm and during atrial pacing at higher levels than those expected in the subsequent experiments. The measurements were repeated under the following series of maneuvers: 1) rapid vena caval occlusion by inflating the hydraulic cuff occluder for 30 seconds and repeated three times with intervals of over 3 minutes; 2) intravenous sodium nitroprusside infusion (0.2–0.5 mg/min); and 3) intravenous rapid infusion of warm 5% dextran (300–400 ml) over 3–5 minutes with subsequent intravenous methoxamine injection (1–2 mg/min).

Each intervention was terminated within 10 minutes, and an adequate recovery time was allowed between each intervention. We checked the drift of the baseline of the high-fidelity micromanometer throughout the study by means of dynamic matching to the fluid-filled catheter pressure externally connected to a Statham P23Db strain gauge manometer (Gould, Cleveland, Ohio). The zero-pressure level was determined at the midventricular level. Calibration of the pulse-transit sonomicrometer was obtained by substituting an electronically generated time delay into a circuit (Triton Technology, San Diego, California). All data were recorded on an eight-channel, forced-ink oscillograph (model 142-8, San-Ei Instruments, Japan) at the paper speed of 100 mm/sec, and stored on magnetic tape with a TEAC recorder (model SR-30, Montabello, California).

Data Analysis
Left ventricular end-diastolic segment length (LVLed) was taken at the nadir of the pressure tracing after atrial contraction (when the first derivative of left ventricular pressure [LV dP/dt] crossed zero), and left ventricular end-systolic length (LVLes) at the nadir of the segment tracing. We defined the left ventricular dimension at left atrial end diastole as LVLa. In each dog, the values of the segment length were normalized to 10 mm baseline end-diastolic length in the control stage. Stroke excursion of the left ventricular segment was corrected by LVLed and expressed as percentage of shortening (%ΔL). Increases in left ventricular segment length during the active atrial contraction were calculated as the percent change from LVLa to LVLed (%ΔLa). The mean velocity of circumferential fiber shortening (LV meanVcf) was obtained by dividing the stroke excursion by ejection period corrected for LVLed.9

Left atrial end-diastolic diameter (LADed) was measured at the diameter immediately preceding atrial shortening following the P wave of the electrocardiogram, indicated by the arrow in Figure 1. The percentage of shortening of the left atrial diameter (%ΔD) was calculated as the excursion from LADed to the nadir of the diameter (LADes) normalized by LADed. The left atrial mean velocity of circumferential fiber shortening (LA meanVcf) was calculated as the ratio of stroke excursion to LADed divided by the left atrial ejection time (the time required from LADed to LADes).10 The shortening characteristics of the left atrium were measured at equal left ventricular end-diastolic pressure (10.0 ± 2.0 mm Hg).11,12 With vena caval occlusion, left atrial pressure and diameter gradually decreased until stable minimal values were attained, usually within 30 seconds. We repeated the above procedure three successive times, and the minimal diameter (Do) and the concomitant pressure (Po) were averaged. The former was considered to approximate the diameter at zero stress.13

The left atrial pressure and diameter signals recorded on the magnetic tape were digitized at 5-msec intervals, and a plot of pressure versus length for one cardiac cycle was obtained by a NEC-9801 computer (Japan) (Figure 2A). The loops were obtained during active expiration at different loading conditions10 (Figure 2B). The atrial diameter was normalized to a natural strain as e = ln (D/Do), where e is the strain, D is the instantaneous left atrial diameter, and Do is the diameter at zero stress. The atrial diastasis was defined as the period when dε/dt was equal to or less than 0.05 sec−1.14 The passive elastic characteristics of the left atrial chamber were assessed by pressure and diameter relation during atrial diastasis (Figure 2C). Using a nonlinear regression algorithm based on an iteration procedure, the data were fitted to an exponential relation as P = αeβt + Co, where P is left atrial pressure (mm Hg), α is elastic constant (mm Hg), β is constant of left atrial chamber stiffness (mm−1), D is left atrial diameter (mm), and C is asymptote pressure (mm Hg). The booster function of the chamber in each cardiac cycle was expressed by the area enclosed by the initial counter-clockwise loop (A loop)7 (Figure 2A).

Pathological Examination
Biopsy specimen of the left atrial wall was fixed in 10% formalin. The tissue was embedded in paraffin and sectioned at a thickness of 3 μm. The sections were stained with hematoxylin-eosin and Masson-trichrome.

Using a general-purpose color image processor (model VIP-21, Olympus, Japan) with the aid of a light pen, the myocardial fiber diameter and the percent area of fibrosis (% fibrosis) were semiautomatically measured at a magnification of 1,200, as described previously.18,19 In brief, the fiber diameter was taken as the diameter at the level of the nucleus. Since the fiber diameter increases from the subepicardium to the subendocardium, 100 myocytes were measured transmurally in each preparation. The area of fibrosis was determined in the Masson-trichrome stain preparation by circling around connective tissues and was expressed as a percent of the image field. For each tissue preparation, measurements were performed in 10 image fields and then averaged.
Figure 2. Panel A: Representative pressure-diameter loop of left atrium (LA) digitized at 5-msec intervals. The left atrial end-diastole is indicated by a symbol (⊕), and the direction of rotation by arrows. The loop rotates counterclockwise initially with active atrial contraction (A loop; a), and then clockwise due to atrial expansion during ventricular systole (v), giving rise to a figure-eight inscription. The area of A loop was defined as an atrial work index. Panel B: The superimposed atrial pressure-diameter loops at basal, during nitroprusside infusion (NP), after volume loading by rapid dextran infusion (VL), and during methoxamine infusion after volume loading (VL + MX). The reduced booster function of the atrium during methoxamine infusion is evident by the decreased area of A loop. Panel C: Passive left atrial pressure-diameter relations (large dots) fitted to a monoexponential curve (small dots) obtained at diastasis periods during passive atrial filling (ascending portion of v wave) were selected over the entire physiological range of left atrial pressure. Lower panel: Distribution of residuals between individual data points and the monoexponential curve determined by a non-linear regression analysis. The residuals distribute randomly: $\text{sr}(\text{MSE})$, sum of residuals squared.
Statistics
Statistical analysis of the time-course of chronic volume overload was made using the Newman-Keuls multiple comparison test with the two-way analysis of variance. The level of statistical significance was \( p < 0.05 \), and the data are presented as the mean ± SD.

Results
Tracings illustrating the variables measured are reproduced in Figure 1, and hemodynamic data are summarized in Table 1. One week after the production of mitral regurgitation, spontaneous heart rates increased by 18% and remained elevated throughout the study period. Hemodynamic and dimensional analyses were carried out in each dog at comparable heart rates achieved by right atrial pacing.

Left Ventricular Hemodynamics (Figure 3)
After the onset of mitral regurgitation, left ventricular pressure did not change in peak value (LVPpeak); however, it declined more rapidly during ejection. Left ventricular end-diastolic pressure (LVPed) was elevated from 6 to 16 mm Hg in the early stage but was reduced to 11 mm Hg in the late stage. LVLed was progressively augmented by 7% in the early stage and by 10% in the late stage. There were progressive increases in the extent of wall shortening. Percentage expansion of the left atrial contraction (%ΔLa) remained the same throughout the study. Thus, the absolute amount of ventricular filling associated with atrial contraction was presumed to be augmented.

Left Atrial Hemodynamics (Figure 4)
In the early stage of mitral regurgitation, mean left atrial pressure (LAPmean) increased from 4 to 12 mm Hg with prominent \( a \) and \( v \) waves. Left atrial end-diastolic diameter (LAded) was augmented by 7.0%. Maximum left atrial stress index during passive atrial filling was triply augmented. Left atrial mean velocity of circumferential fiber shortening (LA meanVcf) increased by 17%. In the late stage, LAPmean decreased to 8 mm Hg with a reduction of the maximum left atrial stress index, while LAded continued to increase by 9.6% of the control value. LA meanVcf tended to decrease, but this change was not statistically significant.

Left Atrial Passive Elastic Pressure-Diameter Relations
The variations between the ascending limb of \( v \) wave of the atrial pressure and the corresponding atrial diameter of several beats obtained at different loading conditions were fitted to a monoequation: \( P = \alpha e^{\beta D} + C_0 \) with a nonlinear regression analysis (Figure 2). Visual inspection of computer plots of the residuals revealed them to be randomly distributed in all cases. The calculated curves of the elastic pressure-diameter relations are shown in Figure 5. The relation was gradually shifted to the right in the chronically volume overloaded atrium. Derived elastic constants are shown in Table 2. The constant of left atrial chamber stiffness (\( B \)) decreased gradually. Elastic constant expressed as a logarithmic form \(( -\ln \alpha ) \) also reduced in a parallel manner with \( B \). The asymptote pressure (Co) did not change throughout the course (Table 2).

The unstressed diameter of the left atrium in the stable minimal state of vena caval occlusion (D0) was augmented by 4.0% in the early and by 8.4% in the late stage of mitral regurgitation. The averaged left atrial diastolic transmural pressure (Po) at the point where D0 was measured was unchanged at each measurement.

Left Atrial External Work-Diameter Relations
In Figure 6, the left atrial external work index (an area enclosed within the A loop, mm-mm Hg) is plotted against LAded. When LAded was increased by acute volume expansion in the control stage, the external work of the left atrium was augmented by 105% together with an enhanced active atrial contraction; the maximum external work (max Work) being achieved when LAded was increased from the control value of 37.7 to 40.8 mm (maxD). Further stretch of the atrial
TABLE 1. Effects of Mitral Regurgitation on Hemodynamic Measures

<table>
<thead>
<tr>
<th></th>
<th>Control stage</th>
<th>Early stage of MR</th>
<th>Late stage of MR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>94 ±12</td>
<td>111 ± 8†</td>
<td>108 ± 10†</td>
</tr>
<tr>
<td>PQ interval (msec)</td>
<td>113 ± 14</td>
<td>112 ± 16</td>
<td>108 ± 14</td>
</tr>
<tr>
<td>Left ventricular measures at basal stage (n = 5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ped (mm Hg)</td>
<td>6 ±2</td>
<td>16 ± 3†</td>
<td>11 ± 3†§</td>
</tr>
<tr>
<td>Ppeak (mm Hg)</td>
<td>111 ± 14</td>
<td>107 ± 8</td>
<td>111 ± 11</td>
</tr>
<tr>
<td>dP/dt (mm Hg/sec)</td>
<td>2,608 ± 324</td>
<td>3,246 ± 546†</td>
<td>3,432 ± 377†</td>
</tr>
<tr>
<td>La(mm)</td>
<td>9.6 ± 0.2</td>
<td>10.4 ± 0.4*</td>
<td>10.5 ± 0.4*</td>
</tr>
<tr>
<td>Led (mm)</td>
<td>10.0</td>
<td>10.7 ± 0.6*</td>
<td>11.0 ± 0.6*þ</td>
</tr>
<tr>
<td>Les (mm)</td>
<td>7.8 ± 0.5</td>
<td>8.0 ± 0.5</td>
<td>8.1 ± 0.3</td>
</tr>
<tr>
<td>%ALA</td>
<td>3.9 ± 1.7</td>
<td>3.5 ± 1.5</td>
<td>3.8 ± 2.1</td>
</tr>
<tr>
<td>%AL</td>
<td>22.3 ± 6.2</td>
<td>25.1 ± 7.2*</td>
<td>25.8 ± 6.3*</td>
</tr>
<tr>
<td>Mean Vcf (circ/sec)</td>
<td>1.41 ± 0.41</td>
<td>1.71 ± 0.48†</td>
<td>1.79 ± 0.46†</td>
</tr>
<tr>
<td>Left atrial measures at basal stage (n = 7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pa (mm Hg)</td>
<td>6 ±2</td>
<td>16 ± 4†</td>
<td>11 ± 4†§</td>
</tr>
<tr>
<td>Pv (mm Hg)</td>
<td>5 ±2</td>
<td>15 ± 4†</td>
<td>12 ± 3†‡</td>
</tr>
<tr>
<td>Pmean (mm Hg)</td>
<td>4 ±1</td>
<td>12 ± 3†</td>
<td>3 ± 3†‡</td>
</tr>
<tr>
<td>Dcd (mm)</td>
<td>37.3 ± 3.9</td>
<td>40.3 ± 4.0†</td>
<td>41.3 ± 4.3†‡</td>
</tr>
<tr>
<td>Des (mm)</td>
<td>34.9 ± 4.2</td>
<td>36.7 ± 3.9†</td>
<td>37.9 ± 4.1†§</td>
</tr>
<tr>
<td>Dv (mm)</td>
<td>37.4 ± 3.9</td>
<td>40.7 ± 4.0†</td>
<td>41.4 ± 4.2†‡</td>
</tr>
<tr>
<td>%ΔD</td>
<td>7.3 ± 3.3</td>
<td>9.3 ± 1.4</td>
<td>8.2 ± 1.6</td>
</tr>
<tr>
<td>Work Index (mm Hg-mm)</td>
<td>11 ± 7</td>
<td>21 ± 11*</td>
<td>20 ± 12*</td>
</tr>
<tr>
<td>Peak Stress Index (mm Hg-mm)</td>
<td>188 ±93</td>
<td>623 ± 183†</td>
<td>490 ± 142†‡</td>
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<tr>
<td>Left atrial measures during acute changes of loading condition (n = 7)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>mean Vcf (circ/sec)</td>
<td>1.03 ± 0.35</td>
<td>1.21 ± 0.30*</td>
<td>1.13 ± 0.20</td>
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<tr>
<td>maxD (mm)</td>
<td>40.3 ± 4.2</td>
<td>42.2 ± 4.2†</td>
<td>43.5 ± 3.8†§</td>
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<tr>
<td>max Work Index (mm Hg-mm)</td>
<td>22.6 ±12.7</td>
<td>33.2 ± 8.5†</td>
<td>39.5 ± 14.9†</td>
</tr>
</tbody>
</table>

Data are presented in mean ± 1 standard deviation. *p<0.05, †p<0.01 = significantly different from control stage. §p<0.05, †p<0.01 = significantly different from early stage.

For definitions of left atrial Work Index, max Work Index, and Peak Stress Index see the text.

MR, mitral regurgitation; Ped, left ventricular end-diastolic pressure; Ppeak, left ventricular systolic peak pressure; dP/dt, peak velocity of left ventricular pressure rise; La, left ventricular segment length at left atrial end-diastole; Led, left ventricular end-diastolic segment length; Les, left ventricular end-systolic segment length; %ΔLa, percent expansion of left ventricular segment length during atrial contraction; %ΔL, percent systolic shortening of left ventricular segment length; mean Vcf, mean velocity of circumferential fiber shortening corrected for end-diastolic circumference; Pa, left atrial pressure at the peak of a wave; Pv, left atrial pressure at the peak of v wave; Pmean, mean left atrial pressure; Dv, left atrial diameter at atrial end-diastole; Des, left atrial diameter at nadir of active shortening; Dv, left atrial diameter prior to passive atrial emptying; %ΔD, percent shortening of left atrial diameter in active contraction; maxD, left atrial end-diastolic diameter at which the maximum value of left atrial work index was achieved.

Histological Findings of the Left Atrial Myocardium (Table 3)

The weights of the seven excised hearts at the end of study significantly exceeded the estimated control values.7 Left atrial myocardial fibers had consistently increased in diameter from 13.2 to 14.4 μm during the sustained mitral regurgitation. The percent fibrosis did not show a significant difference during the course. Inflammatory cell infiltration or hyalinoid degeneration of myocytes were not observed in any specimens.

Discussion

We measured the atrial diameter in conscious dogs, serially, to assess chronic changes in left atrial chamber size in response to chronic mitral regurgitation. However, whether this single measurement adequately expresses the corresponding variation in the atrial size is open to question. Angiographic studies of Gribbe et al.21 demonstrated that the left atrial cavity possessed a spherical shape and contracted in an eccentric fashion. Tsakiris et al.22 assessed the variability in multiple diameters of the left atrium throughout the cardiac cycle and concluded that atrial filling and emptying is
characterized by essentially an equal magnitude of expansion or shortening of circumferential diameters and anteroposterior axes. Goldman et al. noted in conscious dogs that in response to phenylephrine infusion, the left atrial motion was virtually identical in both anteroposterior and lateral diameters during left atrial distension. In a clinical study, identical correlations were shown to exist between angiographically determined left atrial anteroposterior minor axes and the left atrial volume in both the normal and volume overloaded left atrium with a wide variety of lesions. All these data verify the postulation that any left atrial dimension should be sufficient to evaluate the chamber size, particularly when sequential changes are to be assessed serially in a single animal. The similarity of the phasic pattern of atrial diameter to directly measured flow across the mitral valve also lends support to the idea that such measurements can serve as an indicator of global performance of the left atrium.

The comparison of mechanical function of the left atrium and the left ventricle in the conscious dog revealed no appreciable differences at rest, though the velocity of left atrial shortening was more sensitive to an increase in afterload. The atrial myocardium has also been shown to be analogous to the ventricular muscle in that it behaves according to the Frank-Starling mechanism. In the present experiment, by delineating the resting length-tension relation by ascending limb of v wave of the left atrial pressure and corresponding diameter change in several beats in acutely altered preload, we found that the relation between left atrial pressure and chamber diameter in the resting state was essentially monoexponential (Figure 2C). Inertial or viscous properties appear to influence left atrial chamber compliance significantly. However, we tried to minimize these effects by using the data only when strain rate was equal to or less than 5%.

We found that the chamber stiffness constant of the left atrium progressively decreased along with the course of chronic volume overload. This finding indicates that the left atrium became more compliant as a chamber and constitutes one aspect of left atrial adaptation to a chronically sustained volume overload. An increment in left atrial diameter resulted in a smaller pressure rise, thereby keeping the pulmonary venous pressure low and flat. Moreover, with rapid vena caval occlusions, there was a progressive increase in the diameter under unstressed conditions after production of mitral regurgitation. Thus, the pressure-diameter relation not only flattens with larger volumes but also shifts to the right. This anatomical increase in the reservoir volume constitutes a second aspect of the left atrial adaptation.

A similar shift in the pressure-volume relation was noted in cases of volume overloaded ventricles in man. These results are consistent with what one would expect from the observation of Glanz and Kernoff, that chamber dilatation alters location and shape of the pressure-volume curve in such a way that an increase in the unstressed volume is associated with a shift of the curve to the right, with more flattening.

However, McCullagh et al demonstrated that chronic volume overload to the left ventricle is associated with an increase in the ventricular diastolic stiffness, despite a concomitant shift to the right of the pressure-diameter curve. These observations may be partly due to an increase in muscle stiffness along with hypertrophy, compression of the left ventricle by the overloaded right ventricle, or some ischemia complicated with hypertrophy of the ventricle. But, these investigators defined an index of diastolic stiffness as the slope of the calculated linear pressure-diameter curve instead of a monoeXponential curve fitting. When we used a similar linear fitting in the present experiment, the averaged stiffness indices substantially increased from 3.02 mm Hg/mm in the control to 3.28 mm Hg/mm in the "late" stage of mitral regurgitation. Thus, the different conclusion regarding the time-dependent change in diastolic chamber compliance during sustained volume overload is probably due to differences in the models of curve fitting.

In isolated rabbit atria, the pressure-volume characteristics are affected by contractions at a constant volume

![Figure 4](http://circres.ahajournals.org/)

**Figure 4.** Average data showing serial changes in mean left atrial pressure (meanLAP), left atrial end-diastolic diameter (LADed), peak left atrial wall stress index during filling period, and left atrial circumferential fiber shortening (LA meanVcf) at equal left ventricular end-diastolic pressure (10 ± 2 mm Hg). Early, early stage of mitral regurgitation; Late, late stage of mitral regurgitation; NS, not significant.
TABLE 2. Derived Constants of the Left Atrial Pressure-Diameter Relation

<table>
<thead>
<tr>
<th>Dog</th>
<th>Po (mm Hg)</th>
<th>Do (mm)</th>
<th>( -1/na )</th>
<th>( \beta (\text{mm}^{-1}) )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C</td>
<td>E</td>
<td>L</td>
<td>C</td>
</tr>
<tr>
<td>Kk</td>
<td>-5</td>
<td>-5</td>
<td>-4</td>
<td>22.4</td>
</tr>
<tr>
<td>Ck</td>
<td>-2</td>
<td>-2</td>
<td>-2</td>
<td>26.4</td>
</tr>
<tr>
<td>Yk</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>36.0</td>
</tr>
<tr>
<td>Kn</td>
<td>-2</td>
<td>-1</td>
<td>-2</td>
<td>31.6</td>
</tr>
<tr>
<td>Pt</td>
<td>-5</td>
<td>-4</td>
<td>-5</td>
<td>33.7</td>
</tr>
<tr>
<td>Lk</td>
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<td>-1</td>
<td>0</td>
<td>31.7</td>
</tr>
<tr>
<td>Bt</td>
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<td>-3</td>
<td>26.0</td>
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<tr>
<td>Mean</td>
<td>-3</td>
<td>-2</td>
<td>-2</td>
<td>29.7</td>
</tr>
<tr>
<td>SD</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>4.9</td>
</tr>
</tbody>
</table>

Po, left atrial pressure corresponding to Do; Do, left atrial unstressed diameter; \( \alpha \), elastic constant of left atrial pressure-diameter relation; \( \beta \), left atrial chamber stiffness; \( \Gamma \), calculated asymptote pressure; VMSE, the square root of the mean squared error of the observed and predicted values of the exponential curve; C, control stage; E, early stage of mitral regurgitation; L, late stage of mitral regurgitation; SD, standard deviation. *\( p<0.05 \), †\( p<0.01 \) = significantly different from control stage. ‡\( p<0.05 \), §\( p<0.01 \) = significantly different from early stage.

FIGURE 5. Serial changes in the left atrial passive pressure-diameter curve delineated by the ascending limb of V wave and the corresponding diameter change after the production of mitral regurgitation in a representative dog. The sustained volume overload time-dependently moves the curve to larger diameters and flattens it. Closed circles show unstressed pressure-diameter relations determined during vena caval occlusions (Po, Do). C, control stage; E, early stage of mitral regurgitation; L, late stage of mitral regurgitation; and LA, left atrial.
The discrepancy between atrial size and pressure
gitation have been characterized in patients with little
volume overload, new sarcomeres are added in series
support the proposal of a significant role of hypertrophy
reflects a change in compliance of the left atrium, and
elevated left atrial pressure at the opposite end.34-38-3'
enlargement of the left atrium and normal or slightly
by those with severe mitral regurgitation with massive
enlargement of the left atrium but a marked elevation
of increase in the unstressed diameter throughout the
experimental course cannot entirely be explained by this
phenomenon.35
It has been postulated that, in the presence of chronic
volume overload, new sarcomeres are added in series
in order to normalize elevated end-diastolic stress
resulting in eccentric hypertrophy with fiber elongation
and chamber enlargement.36J7 The same mechanism
may also account for the observed increase in the
unstressed left atrial diameter. We observed a definite
increase in the diameter of left atrial myocytes 4 weeks
after the onset of mitral regurgitation. These findings
support the proposal of a significant role of hypertrophy
in the progressive increase in the unstressed diameter.

Hemodynamic and clinical pictures of mitral regur-
gitation have been characterized in patients with little
enlargement of the left atrium but a marked elevation
in left atrial pressure at one end of the spectrum, and
by those with severe mitral regurgitation with massive
enlargement of the left atrium and normal or slightly
elevated left atrial pressure at the opposite end.52.53 The
discrepancy between atrial size and pressure
reflects a change in compliance of the left atrium, and
rather than contractions against a constant pressure,
indicating that creep and hysteresis are essential to the
determinants of the atrial volume at a given pressure.25
It is possible that the observed increase in Do might be
accompanied by creep; however, a continuous manner
of increase in the unstressed diameter throughout the
experimental course cannot entirely be explained by this
phenomenon.35

It was suggested that long-standing mitral regurgitation
might modify the mechanical characteristics of the
atrial wall.2 Our data provide additional support to the
above clinical observations and clearly indicate that
diastolic properties of the left atrium are determined by
loading conditions in the chamber. Hence, there is an
important compensatory mechanism to modify preload
on the left ventricle.

With acute volume expansion in the intact heart, left
atrial performance was initially augmented until the
distension reached 8% over the control value, subse-
sequently further distension resulted in a decrease in atrial
shortening. It has been explained that at this point, the
limit of the preload reserve was attained and afterload
mismatch ensued. Therefore, the conduit function
predominated the booster pump function.24 Thus, the
augmentation of the atrial work after the sustained
mitral regurgitation is related to a gradual increase in

### Table 2. (Continued)

<table>
<thead>
<tr>
<th>Co (mm Hg)</th>
<th>VMSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>E</td>
</tr>
<tr>
<td>0.8</td>
<td>-0.5</td>
</tr>
<tr>
<td>-3.8</td>
<td>-2.8</td>
</tr>
<tr>
<td>1.5</td>
<td>-7.2</td>
</tr>
<tr>
<td>-2.0</td>
<td>4.8</td>
</tr>
<tr>
<td>-5.0</td>
<td>-1.9</td>
</tr>
<tr>
<td>-0.4</td>
<td>0.3</td>
</tr>
<tr>
<td>-0.5</td>
<td>0.2</td>
</tr>
<tr>
<td>-1.3</td>
<td>-1.0</td>
</tr>
<tr>
<td>2.4</td>
<td>3.6</td>
</tr>
</tbody>
</table>

### Table 3. Morphological Comparisons Between Before and After Chronic Mitral Regurgitation

<table>
<thead>
<tr>
<th>Dog</th>
<th>Body weight (kg)</th>
<th>Days after MR (days)</th>
<th>Heart weight (gm)</th>
<th>Size of left atrial myocytes (μm)</th>
<th>% fibrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control (estimated)</td>
<td>End of study</td>
<td>Before MR</td>
<td>End of study</td>
<td>Before MR</td>
</tr>
<tr>
<td>KK</td>
<td>21</td>
<td>20</td>
<td>138</td>
<td>147</td>
<td>10.3±2.3</td>
</tr>
<tr>
<td>CD</td>
<td>20</td>
<td>20</td>
<td>132</td>
<td>159</td>
<td>11.4±2.3</td>
</tr>
<tr>
<td>YK</td>
<td>35</td>
<td>23</td>
<td>231</td>
<td>244</td>
<td>13.1±2.9</td>
</tr>
<tr>
<td>KN</td>
<td>28</td>
<td>24</td>
<td>158</td>
<td>289</td>
<td>16.5±3.0</td>
</tr>
<tr>
<td>PT</td>
<td>25</td>
<td>21</td>
<td>165</td>
<td>257</td>
<td>13.5±2.6</td>
</tr>
<tr>
<td>LK</td>
<td>25</td>
<td>29</td>
<td>165</td>
<td>266</td>
<td>15.2±3.1</td>
</tr>
<tr>
<td>BT</td>
<td>22</td>
<td>35</td>
<td>145</td>
<td>212</td>
<td>12.3±1.9</td>
</tr>
<tr>
<td>Mean±SD</td>
<td>25±5</td>
<td>25±4</td>
<td>162±33</td>
<td>225±54</td>
<td>13.2±2.0</td>
</tr>
</tbody>
</table>

The control heart weight was estimated by multiplying body weight by 6.6.7 MR, mitral regurgitation; SD, standard deviation; NS, not significant.
preload of the left atrium. This may also be the result of development of hypertrophy associated with chamber enlargement and which serves to accommodate the increased diastolic volume and to correct acute afterload mismatch by reducing wall stress of the left atrium.

Certain limitations of the present experiment should be given attention. Owing to the difficulties in keeping the severely overloaded animals chronically alive, the severity of mitral regurgitation was rendered relatively modest. In the clinical setting, much severer cases are often encountered with more prominent v wave. Previously, we studied dynamic geometry of such severe mitral regurgitation in the acute open chest experiment, in which we showed that severe mitral regurgitation placed the atrium on a higher portion of its pressure diameter curve where the functional compliance was reduced and reflected in a larger v wave.2

Though the degree of hypertrophy was mild in the present study, a considerable thickening of the left atrial wall has been actually documented in autopsied patients who had had severe mitral regurgitation secondary to ruptured chordae tendineae.40 In these cases, hypertrophy may well cause a decrease in compliance when hypertrophied myocardium is accompanied by an alteration in the material properties. The present model is not relevant to these pictures of clinical mitral regurgitation.

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**Key Words** • left atrium • chronic mitral regurgitation • chamber compliance • Frank-Starling mechanism
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