

# Altered Left Ventricular Chamber Stiffness and Isovolumic Relaxation in Dogs With Chronic Pulmonary Hypertension Caused by Emphysema

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**Background.** In chronic obstructive lung disease, a right to left ventricular septal shift that occurs as a consequence of right ventricular pressure overload is the usual mechanism given to explain a decrease in left ventricular (LV) diastolic performance. The purpose of the present study was to examine the extent to which this mechanism could account for a decrease in LV diastolic function in a canine model in which pulmonary artery pressure was elevated to a level found in human disease.

**Methods and Results.** Severe emphysema was produced in dogs by repeated instillations of the enzyme papain into the lung. To assess LV diastolic function, we used sonomicrometry, in which three pairs of subendocardial crystal transducers were implanted along the three orthogonal axes of the LV. LV end-diastolic dimensions and pressure-strain relations along the three axes, as well as the time constant of LV isovolumic relaxation (T), were measured before (baseline) and after 1 year of emphysema (post-1-year study). The results showed that after 1 year of pulmonary hypertension, LV pressure-strain relations were decreased along the septal-lateral and anterior-posterior axes, but a right to left ventricular septal shift was not detected. The relation of average midwall circumferential stress to midwall circumferential strain was used to describe the intrinsic compliance of the LV. The results showed that myocardial stiffness increased in emphysema but that chamber volume was not reduced. At the post-1-year study, T was abnormally increased in the emphysema group in response to augmented preload and afterload compared with preemphysema measurements.

**Conclusions.** We conclude that mechanisms other than ventricular interdependence may be operative in leading to altered LV diastolic filling in chronic emphysema. (*Circulation* 1993;87:247-260)

**KEY WORDS** • diastole • myocardial stiffness • lung • myocardial relaxation • cor pulmonale

In chronic obstructive pulmonary disease (COPD), although the left ventricle (LV) is spared from direct involvement by the pathological process, LV diastolic performance may be decreased because of the load imposed on the right ventricle (RV). Ventricular interdependence is the usual mechanism cited for this finding.<sup>1</sup> Because the ventricles are enclosed by the semirigid pericardial sac and because RV end-diastolic pressure (RVEDP) may increase in COPD, the transventricular pressure gradient may favor a relative shift in the septum toward the LV. Since the septum would now encroach on the LV cavity, LV volume would be reduced for a given LV end-diastolic pressure (LVEDP).

However, another less frequently cited mechanism that may also be important in this condition involves a change in LV material properties that may evolve with chronic RV pressure load and that may lead to a

decrease in LV diastolic compliance.<sup>2-4</sup> Although the mechanism is not clear, Laks et al<sup>4</sup> found that when pulmonary artery banding was performed in dogs, pulmonary hypertension caused a remodeling of the LV that was not confined to the interventricular septum but affected the global LV. They noted that pulmonary artery banding not only caused a decrease in LV diastolic compliance but also resulted in both RV and LV diastolic dilation caused by changes in myocardial cell and sarcomere lengths.<sup>4-6</sup> These investigators postulated that pulmonary artery banding caused an initial dilation of the ventricular chambers, which, if sustained, stimulated myocardial hypertrophy that subsequently led to a decrease in LV chamber volume. Based on the latter study, LV remodeling would be a dynamic process that could lead to altered diastolic performance in COPD.

To better define the changes in cardiac function that occur in COPD, we developed an animal model of emphysema in which pulmonary artery pressures could be increased to a level found in human disease.<sup>7</sup> In an initial study, we observed that after approximately 3 months of emphysema-induced pulmonary hypertension, LV performance was unchanged compared with preemphysema measurements.<sup>7</sup> However, because changes in LV diastolic function may evolve over a prolonged interval, we examined LV diastolic performance in our emphysema model about 1 year after the lung lesion was

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produced. The changes in LV mechanics in chronic emphysema were then contrasted with those observed in a model of acute pulmonary hypertension to better understand the long-term effect of RV pressure overload on LV diastolic performance in emphysema.

## Methods

### Overall Protocol

The experimental design of this study necessitated five components. In component 1 ("Chronic Emphysema Study"), LV diastolic mechanics were examined in 10 emphysema and 10 control dogs over a 1-year interval in which ultrasonic crystal techniques were used to measure LV dimensions in five animals in each group. Components 2, 3, and 4 are included under the heading of "Additional Emphysema Experiments." In component 2, we describe supplemental experiments performed in a subset of these 10 emphysema dogs to exclude inaccuracies in the measurement of pleural surface pressure from affecting the results. In component 3, to corroborate LV findings observed with ultrasonic crystals, we used radionuclide angiography techniques to assess LV geometry in five of these emphysema dogs. In component 4, we examined whether our method of producing emphysema could directly affect LV diastolic function. Finally, in component 5, included under the heading of "Acute RV Pressure Overload Experiments," we contrasted the LV diastolic changes found in chronic emphysema with those caused by acute pulmonary hypertension.

### Chronic Emphysema Study (Component 1)

**Emphysema model.** Emphysema was produced by repeated intrabronchial instillations of the enzyme papain into the lung, in which the procedure was identical to that previously described.<sup>7,8</sup> Briefly, mongrel dogs ( $n=10$ ) weighing 20–30 kg were anesthetized with sodium pentobarbital (30 mg/kg) and intubated with an endotracheal tube. About 4 cm<sup>3</sup> of the enzyme papain (Type IV, Sigma Chemical Co., St. Louis, Mo.) mixed in about 36 cm<sup>3</sup> of normal saline solution was placed into one of the lower lobes. About seven instillations were placed into each lower lobe; instillations were performed approximately every week and were altered between the lower lobes. Immediately after the instillation, the animals were ventilated for 6–7 hours and then returned to their cages. They received antibiotics (penicillin and gentamicin) before each instillation and every 12 hours thereafter for a total of four doses to prevent bacterial infection.

As assessed by pulmonary function tests, evidence of emphysema is observed at about 1 week after the lobe is instilled with papain, and the pulmonary lesion is not progressive once instillations of the enzyme have stopped.<sup>7,8</sup>

In control dogs ( $n=10$ ), the protocol was identical to that performed in the emphysema dogs, except that 40 cm<sup>3</sup> of normal saline solution rather than papain was administered into the lower lobes at weekly intervals. The dogs were randomly allocated to either of the two groups.

**Animal preparation.** Two months before baseline measurements (preemphysema) were obtained, surgery was performed on the animal to implant three pairs of

subendocardial ultrasonic crystal transducers into the LV to measure dimensions (piezoelectric crystals: hemispheric ceramic transducers, Channel Industries, Santa Barbara, Calif.).<sup>8–10</sup> The methodology was similar to that previously described.<sup>11</sup> Subendocardial crystal pairs were placed along the anterior-posterior (AP) and septal-lateral (SL) minor axes and apex-to-base (AB) major axis of the LV to be used later for recording LV end-diastolic dimensions (LVEDD). Respective high-fidelity pressure transducers (P 6.5, Konigsberg Instruments, Inc., Pasadena, Calif.) were implanted into the RV at the mid portion of its free wall and into the LV at the apex.<sup>9–11</sup> A venous occluder (In-Vivo Metric, Healdsburg, Calif.) was positioned around the inferior vena cava such that when the balloon was inflated, venous return could be severely reduced to obtain multiple LV end-diastolic pressure–dimension coordinates along each axis.

Ten emphysema (emphysema group) and control dogs (control group) were studied. Of the 10 animals in each group, RV and LV pressure transducers were placed in all dogs, and in addition, crystal transducers and a venous occluder were placed in five. Implantation was performed with the animal anesthetized (sodium pentobarbital, 30 mg/kg) and mechanically ventilated (15 ml/kg). Under sterile conditions, a left thoracotomy incision was made, the pericardium was split, and the crystal pairs were placed along the three axes as previously described.<sup>11</sup> The pericardial incision was only loosely sutured closed, so that the LV would be exposed to pleural surface pressure rather than pericardial pressure. The chest wall incision was then closed. Wires connected to the crystal transducers were brought out through the thoracotomy incision and tunneled subcutaneously, exiting at the neck. The animal wore a collar to protect the crystal and pressure transducer wires until the time of study. The animal was returned to its cage and treated with antibiotics for 6 days (cloxacillin and gentamicin). All procedures were approved by the University Animal Care Committee.

After baseline measurements, papain was administered weekly over a 3–4-month period in the emphysema dogs, whereas normal saline solution was administered over similar intervals in control dogs. Final measurements were obtained approximately 1 year after the last dose of papain was given (post-1-year study).

**Pulmonary function measurements.** These measurements were determined to assess changes in lung function between baseline and the post-1-year studies and were taken in a manner previously described.<sup>7</sup> With the animals anesthetized (pentobarbital, 30 mg/kg) and placed into a volume displacement plethysmograph, functional residual capacity was measured by the DuBois technique,<sup>7,8</sup> after which the animal's lungs were inflated to a transpulmonary pressure of 30 cm H<sub>2</sub>O to obtain total lung capacity. Pleural surface pressure ( $P_{pl}$ ) was measured at the baseline and post-1-year studies by the esophageal balloon technique.<sup>7,8</sup>

**Cardiac measurements.** At the baseline and post-1-year studies, LV diastolic function was determined approximately 1 week after pulmonary function tests were obtained. Early and late LV diastolic performances were assessed at respective separate settings about 1 week apart, for which the specific protocols for the two studies are described further below. Measure-

ments were obtained with the animal awake and placed in the prone position.

Early LV diastolic function was assessed by measurement of the rate of isovolumic relaxation, which was analyzed from the LV pressure trace in a manner described by Raff and Glantz.<sup>12</sup> The rate of ventricular relaxation is taken from the isovolumic pressure decay and measures events that occur during the early part of ventricular diastole.<sup>13</sup> Early diastolic changes may or may not be reflected in changes at end diastole. If the rate of ventricular relaxation were significantly prolonged, then the next systole could occur before the preceding diastole was completed. Occurrence of such a process in emphysema could lead to an increase in diastolic stiffness that would be heart-rate and time-constant dependent.<sup>13</sup>

Isovolumic relaxation period can be defined from the time of the maximum rate of LV pressure decline ( $-dP/dt$ ) to the time when LV pressures fall to 5 mm Hg above the end-diastolic pressure of the next beat.<sup>12</sup> If the fall in intraventricular pressure can be analyzed as a monoexponential equation with a time constant  $T$ , then  $P = P_0 e^{-t/T} + P_b$ .<sup>12</sup>  $P$  represents intracavitary pressure,  $P_0$  is the intracavitary pressure at minimum  $dP/dt$ ,  $t$  is time, and  $P_b$  is a constant.  $P_b$  is incorporated into the formula of Raff and Glantz to account for errors resulting from external pressures applied to the heart via the pleura and pericardium and from the fact that the fully relaxed LV may not have a zero pressure.<sup>12</sup>  $T$  was estimated from linear regression analysis in which  $dP/dt$  was plotted against  $P$ . At least four coordinates were used in the calculation. The average  $T$  obtained over 3–4 beats is given for each of the conditions examined.

Late diastolic function was assessed by the relation of LVEDD to LVEDP, which was measured approximately 1 week after measurement of isovolumic relaxation. LVEDD along the three axes was determined by sonomicrometry with the animal lying quietly in the prone position.<sup>8–10</sup> The animal was well acquainted with the laboratory and was breathing slowly enough that measurements could be determined at end expiration.

The ultrasonic crystal transducer technique of measuring ventricular dimensions has been detailed elsewhere.<sup>8–10</sup> The wires from the crystal pairs were attached to a sonomicrometer (Sonomicrometer 120, Triton Technology, San Diego, Calif.) and the outputs displayed on an eight-channel recorder (Hewlett-Packard, 7758A). LVEDD was defined by LVEDP, which in turn was defined as the pressure at which  $+dP/dt$  increased by 150 mm Hg/sec, with the increase sustained for at least 50 msec.<sup>14</sup> Concomitant RVEDP and RV peak systolic pressures (RVESP) were obtained from the RV pressure trace. LV end-systolic pressure (LVESP) was taken from the LV pressure trace and defined as the point in the cardiac cycle at which pressure/dimension was a maximum.<sup>15</sup> To obtain multiple (at least three or four) LVEDD-versus-LVEDP coordinates along each axis before and after emphysema, preload was acutely reduced by occlusion of the vena cava. LV pressure–dimension relations were constructed from these coordinates. Venous occlusion lasted about 4 seconds.

After measurements of late LV diastolic performance were obtained, the animal was anesthetized with pen-

tobarbital (30 mg/kg) and placed in the left lateral decubitus position. A high-fidelity transducer-tipped catheter (Millar Instruments, Houston, Tex.) was advanced first into the LV from a carotid artery incision to calibrate the implanted LV pressure transducer and then into the RV by means of the external jugular vein to calibrate the implanted RV pressure transducer. The Konigsberg transducers were positioned in their respective ventricles during the implantation procedure such that they would approximate the plane at which the Millar catheter would be introduced during calibration. Although it is possible that the recording tips of the Millar and Konigsberg transducers were not precisely positioned at the same horizontal level in all experiments, in a previous study<sup>11</sup> in which an implanted Konigsberg transducer was calibrated by this technique and also by a fluid-filled catheter system implanted immediately adjacent to the Konigsberg transducer as performed in Reference 9, there were no differences in ventricular pressure recordings when the two techniques were compared. This is probably because of the small vertical size of the ventricles with the animal in this position. After transducer calibration, the carotid and jugular vascular accesses were surgically closed.

With the animal still anesthetized and placed in the left lateral decubitus position,<sup>7</sup>  $P_{pl}$  was then measured at functional residual capacity with the esophageal balloon technique. By measuring  $P_{pl}$ , we were able to relate transmural LVEDP ( $LVEDP_{tm} = LVEDP - P_{pl}$ ) to LVEDD.  $P_{pl}$  appeared to be the relevant external pressure in this basically open-pericardial preparation and was used in the calculation of transmural pressures (i.e., vascular pressure minus  $P_{pl}$ ), since emphysema would increase  $P_{pl}$  by decreasing lung elasticity. After the measurement of  $P_{pl}$ , the animal was returned to its cage.

#### *Protocol: Chronic Emphysema Study*

At the baseline study, measurements included pulmonary function tests, indexes of LV isovolumic relaxation, and LV diastolic pressure–dimension relations. These three components were determined on separate occasions about 1 week apart. In the assessment of LV isovolumic relaxation,  $T$  was initially obtained while the animals were quietly resting without prior intervention. Then, to assess the response of  $T$  to an elevation in afterload,  $T$  was determined while phenylephrine was infused to increase LVESP by about 60% ( $n=5$ ).

At the post-1-year study, the same measurements were obtained, except that in the assessment of isovolumic parameters, the response of  $T$  to preload increase was also examined. Volume (20 ml/kg of 6% hetastarch in normal saline solution) was intravascularly infused over a 15-minute period. The sequence of measurements was otherwise exactly the same in the two studies.

#### *Additional Emphysema Experiments (Components 2, 3, and 4)*

In the chronic emphysema study, one initial concern was that  $P_{pl}$  measured with an esophageal balloon may not accurately reflect pressure external to the heart or that the emphysematous lung adjacent to the heart may exert a compressive force that could alter our interpretation of the LVEDP–LVEDD relation (note also that if the pericardium were totally removed during surgery, the heart would adhere to the lung; therefore, we found



that the best approach was to loosely approximate the ends of the cut pericardium).

In component 2 of this study, to assess whether inaccuracies in the measurement of  $P_{pi}$  were responsible for the changes observed after 1 year of emphysema, we performed additional experiments on a separate study day in three of the emphysema dogs included in the chronic emphysema study in which ultrasonic crystal transducers were implanted. LV diastolic pressure–dimension relations were obtained with the chest widely opened and the pericardial–diaphragmatic ligament cut. The animal was anesthetized (pentobarbital, 30 mg/kg) and ventilated (15 ml/kg), and measurements were obtained at end expiration. In these experiments,  $P_{pi}$  would indeed be atmospheric, and the pericardium would be under no external tension. LV diastolic pressure–dimension relations in the open- and closed-chest conditions were compared. In one of these emphysema dogs, moreover, to assess whether pleural surface pressure was indeed pericardial pressure, the pericardium was totally taken off, and the closed-chest, open-chest, and open-pericardium conditions were compared. The animals were killed after this part of the protocol, and heart weights were obtained.

In component 3, we used radionuclide angiography techniques to corroborate aspects of the sonomicrometric LV findings observed in the chronic emphysema study. In those five emphysema dogs in the chronic emphysema study in which ultrasonic crystals were not implanted, radionuclide angiographic techniques were used to determine whether LV diastolic geometry in emphysema was altered by a leftward shift in the ventricular septum. Gated equilibrium radionuclear angiograms were obtained at intervals similar to those described in the chronic emphysema study, in which the methodology was identical to that previously described.<sup>8,9</sup> Briefly, angiograms were obtained after *in vivo* red cell labeling with 40 mCi <sup>99m</sup>Tc after the intravenous administration of stannous pyrophosphate. Under pentobarbital anesthesia (30 mg/kg *i.v.*), the dogs were maintained in the supine position. A mobile gamma camera (Picker Corp., Northford, Conn.) equipped with a parallel hole collimator was oriented approximately in the left anterior oblique position, where the interventricular septum was clearly visible on the oscilloscope display of the blood pool in the heart. Caudal angulation of 5–15° was used as needed to obtain chamber separation. Image acquisition allowed count information to be stored in frames of cardiac cycle (32 per cycle) in a computer (MDS; A<sup>2</sup> hardware and software). The cardiac cycle could be displayed on a hard copy as well as on a video screen that allowed end-diastolic and end-systolic frames to be identified. Each frame contained at least 250,000 counts. LV end-diastolic and end-systolic regions of interest were assigned with a light pen. Background-subtracted time–activity curves were generated for the LV. Separation of the RV and LV from the respective atria was aided by reference to first-pass flow studies recorded in the left anterior oblique position obtained at the beginning of the study to obtain the best views and reference to phase contrast techniques. Ejection fraction was calculated as the difference between end-diastolic and end-systolic counts divided by end-diastolic counts after appropriate background corrections. End-diastolic vol-

ume was calculated from stroke volume divided by ejection fraction, in which stroke volume (cardiac output/heart rate) was measured by a thermodilution Swan-Ganz catheter advanced into the pulmonary artery. Cardiac output was obtained at similar LVEDP between conditions.

In terms of our chronic emphysema study, moreover, we were also concerned that the enzyme papain could directly alter heart function if, during bronchial instillation, papain reached the heart through the pulmonary or bronchial circulation. In component 4, to check for this possibility, five additional control dogs (separate from the other control animals) were studied in which, after baseline measurements of LV isovolumic relaxation and late diastolic function were obtained, papain was administered intravenously (2 cm<sup>3</sup>) and intra-arterially (2 cm<sup>3</sup>). Four cubic centimeters of the enzyme was administered weekly over a 10-week period. The animals were pretreated with steroids and antihistamines to prevent anaphylaxis caused by repeated administrations of the enzyme. Methylprednisolone (40 mg) was given the night before papain administration, whereas methylprednisolone (40 mg) and chlorpheniramine maleate (1 mg/kg) were administered approximately 1 hour before the procedure. Diastolic function was then measured about 1 year after the last dose of intravascular papain was given, for which the protocol was identical to that described in the chronic emphysema study.

#### *Acute RV Pressure Overload Experiments (Component 5)*

A basic aim of this study was to determine whether the LV diastolic findings observed after 1 year of emphysema could be explained simply by a right to left ventricular septal shift as would occur during acute pulmonary hypertension or whether another process had evolved. In component 5 of this study, acute experiments were performed in four additional control dogs (separate from those in the other studies), in which the ends of the cut pericardium were also loosely approximated, to examine the effect of acute pulmonary hypertension on LV diastolic performance in this preparation. In these experiments, pulmonary hypertension was caused by occlusion of the right and left pulmonary arteries with twill tape ½ in. in diameter. The animal was anesthetized (pentobarbital, 30 mg/kg), intubated, and ventilated (15 ml/kg). The chest was widely opened and the pulmonary arteries exposed. Subendocardial crystal transducers were placed along the three axes of the LV. After baseline measurements were obtained, RVPSP was increased to a level similar to that found in the emphysema dogs at the post-1-year study. The changes in LVEDD before and after pulmonary hypertension were compared. The animal was killed at the completion of this experiment.

#### *Data Analysis*

To analyze diastolic force–dimension relations in the various components of this study, each LV dimension was normalized to a Lagrangian strain (*E*) (fractional extension from unstressed dimension).  $E = (D - D_0)/D_0$ , where  $D_0$  is the unstressed dimension of  $D$ . The unstressed dimensions of the three LV axes and of midwall circumference ( $L$ ) were determined at maximal occlu-

sion of the vena cava when transmural LVEDP was zero. The analysis was similar to that described by Visner et al,<sup>3</sup> except that some modifications of the formulas used in Reference 3 were necessary, because Visner et al used predominantly epicardial rather than endocardial crystals.

LV diastolic pressure-strain data were selected from multiple (four to 10) cardiac cycles during occlusion of the vena cava. Data were recorded at end expiration to minimize respiratory variation in the LV pressure-dimension data. These data were fitted by nonlinear least-squares regression to the Kelvin viscoelastic equation<sup>16</sup>:

$$\text{LVEDP}_{\text{tm}} = a(e^{bE} - 1) + n\text{dE}/\text{dt} + G \quad (1)$$

where  $a$ ,  $b$ ,  $n$ , and  $G$  are parameters determined from the curve fit, and  $\text{dE}/\text{dt}$  is strain velocity. Because only data of low strain velocity were used (i.e., data were analyzed at the end of diastole, when filling rates are negligible), the viscous term of equation 1,  $n\text{dE}/\text{dt}$ , was set equal to zero, and only the elastic component of the Kelvin equation was used:

$$\text{LVEDP}_{\text{tm}} = a(e^{bE} - 1) + G \quad (2)$$

LV end-diastolic pressure-strain curves along the three axes were obtained at baseline and after 1 year of emphysema. Strains were computed from the curve fit at  $\text{LVEDP}_{\text{tm}} = 12$  mm Hg, 8 mm Hg, and 4 mm Hg.<sup>3</sup>

To examine the intrinsic stiffness of the LV myocardium, all external constraints, as well as alterations in LV geometry, must be accounted for.<sup>17-19</sup> The relation between average midwall circumferential wall stress and midwall circumferential strain was used to describe the intrinsic compliance of a circumferential myocardial hoop at the equator of the LV. To estimate midwall circumferential stress at the equator of the LV, an effective external LV pressure (ELVP) was calculated with the assumption that two thirds of the surface area of the LV is surrounded by the pleural cavity (since the pericardial incision was loosely approximated) and one third is surrounded by the RV<sup>17</sup> (i.e.,  $\text{ELVP} = [2P_{\text{pl}} + P_{\text{RV}}]/3$ ).

The average midwall circumferential stress ( $\sigma$ ) at the equator of the LV was then calculated for a thin-wall ellipsoid. Average equatorial wall thickness ( $h$ ) was measured from multiple equatorial sections taken at autopsy for each dog. The mean  $h$  obtained in the control group was used for the baseline and post-1-year studies in the latter group and for the baseline value in the emphysema group. The mean  $h$  obtained at autopsy was used for the post-1-year study in the emphysema group (see "Discussion"). For the apex-base axis, wall thickness was taken as 0.55 of mean  $h$ , since it is thinner along this axis.<sup>20</sup>

Flügge<sup>19</sup> has developed expressions for thin ellipsoids that may be modified by use of the appropriate geometry. Mirsky<sup>17</sup> has shown that the Laplace formulas yield reasonable results for the average stresses if one associates endocardial geometry with cavity pressures and epicardial geometry with external pressures as opposed to midwall geometry. Based on the general expressions developed by Flügge, the average circumferential stress<sup>17-19</sup> in the LV at the equator can be given approximately by

$$\sigma = \text{LVEDP}(b)/4h\{(c)/(b) + (b)/(c) - [(b)(c)/(a)^2]\} - \text{ELVP}[(b+2h)/4h]\{[(c+2h)/(b+2h)] + [(b+2h)/(c+2h)] - [(b+2h)(c+2h)/(a+1.1h)^2]\}$$

where  $a$  is apex-base dimension,  $b$  is anterior-posterior dimension, and  $c$  is septal-lateral dimension measured from the subendocardial surfaces.

LV midwall equatorial circumference ( $L$ ) was calculated from

$$L = 2(b+h) \int_0^{\pi/2} \sqrt{1 - k^2 \sin^2 \theta} d\theta$$

where  $k^2 = [(b+h)^2 - (c+h)^2]/(b+h)^2$ .

Midwall circumference strains  $[E = (L - L_0)/L_0]$  at circumferential stresses of 15, 20, and 25 dynes  $\times 10^3/\text{cm}^2$  were determined from the Kelvin elastic equation, where  $\sigma = a(e^{bE} - 1) + G$ . The results were compared before and after emphysema.

To further assess whether an LV septal shift occurred in the chronic emphysema study, an LV eccentricity index was used to quantify relative movement of the ventricular septum during diastole as well as at end ejection at the baseline and post-1-year studies. According to Louie et al,<sup>21</sup> this index is defined by the relation of the anterior-posterior dimension to the septal-lateral dimension. If this ratio increased in the emphysema group at the post-1-year study compared with the baseline study, then this finding would suggest relative narrowing along the septal-lateral dimension and a shift of the ventricular septum toward the LV at the post-1-year study.

Statistics included Student's paired  $t$  test when two levels of a parameter were compared in a single group. A two-way ANOVA for repeated measures was used when two repeated measures were examined in a single group (within-within ANOVA: ANOVA2R2, NWASTATPAK version 4.1, Northwest Analytical, Inc., Portland, Ore.). When results were compared between groups, statistics included Student's unpaired  $t$  test when a nonrepeated parameter was examined; a two-way ANOVA (between-within ANOVA: split-plot design: ANOVA2R1) was used when repeated measurements of a parameter were compared between groups. The specific tests are indicated in the tables and legends to figures. Values are reported as mean  $\pm$  SD.

## Results

In the chronic emphysema study, total lung capacity (mean  $\pm$  SD) increased from  $3.7 \pm 1.1$  l at baseline to  $5.9 \pm 1.7$  l at the post-1-year study ( $p < 0.01$ ), whereas total lung capacity in the control group did not change ( $4.1 \pm 0.9$  l at baseline versus  $4.1 \pm 0.7$  l at the post-1-year study;  $p < 0.01$  between groups).  $P_{\text{pl}}$  was considered in the calculation of cardiac transmural pressures in the individual dogs. Cardiac measurements were obtained at functional residual capacity where there would be just marginal differences in  $P_{\text{pl}}$  between the control and emphysema groups. At the post-1-year study, mean  $P_{\text{pl}}$  in the emphysema group ( $0.4 \pm 1.1$  cm H<sub>2</sub>O) was just slightly more positive than in the control group ( $-0.9 \pm 0.9$  cm H<sub>2</sub>O;  $p < 0.025$ ).

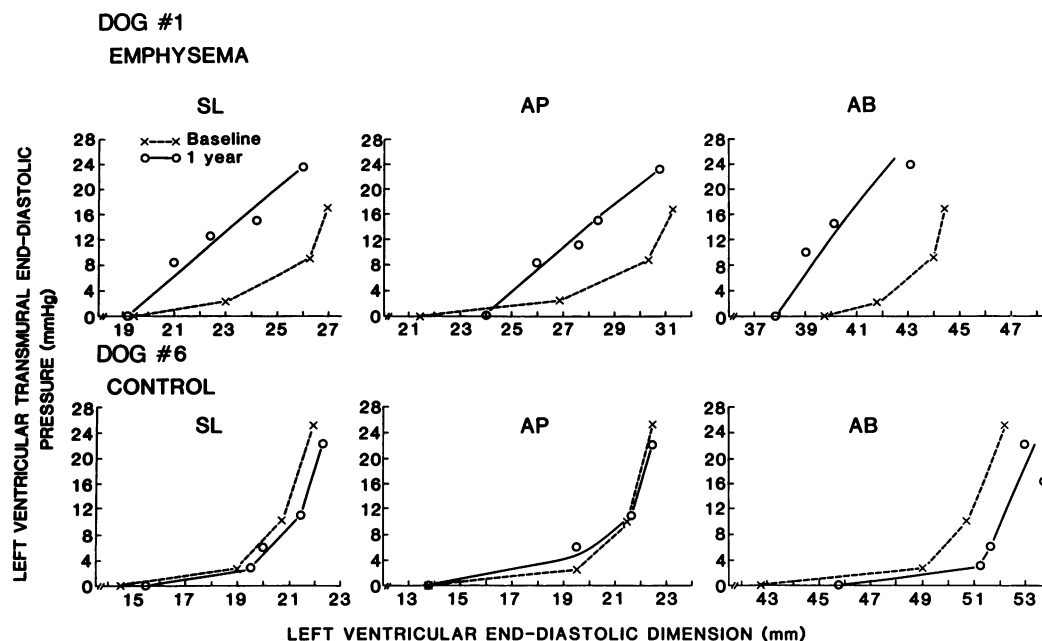


FIGURE 1. Graphs showing left ventricular transmural end-diastolic pressure ( $LVEDP_{tm}$ ) plotted against left ventricular end-diastolic dimension along the septal-lateral (SL) and anterior-posterior (AP) minor axes and the apex-base (AB) major axis in an emphysema dog (upper panel) and control dog (lower panel). In the emphysema group, diastolic compliance at low  $LVEDP_{tm}$  was decreased at the post-1-year study, but absolute dimensions at high  $LVEDP_{tm}$  were unchanged compared with baseline values. Along the AP axis, the dimensional intercept at the post-1-year study was increased compared with baseline. In the control group, there were no changes between the baseline and post-1-year studies.

In the emphysema group,  $RVPSP_{tm}$  increased from  $29 \pm 6$  mm Hg at baseline to  $41.1 \pm 5.1$  mm Hg at the post-1-year study ( $p < 0.05$ ).  $RVPSP_{tm}$  was unchanged in the control group ( $27.4 \pm 5.7$  versus  $27 \pm 5.4$  mm Hg;  $p < 0.05$  between groups).  $RVEDP_{tm}$  tended to increase in the emphysema group over this period ( $4.4 \pm 4.2$  to  $5.8 \pm 1.9$  mm Hg), whereas there was no change in the control group ( $2.5 \pm 2.7$  versus  $2.7 \pm 3.2$  mm Hg;  $p < 0.01$  between groups). Heart rates were unchanged between the baseline and post-1-year studies in both groups. In the emphysema group, respective heart rates were  $111 \pm 23$  versus  $113 \pm 9$  beats per minute, whereas in the control group, heart rates were  $111 \pm 20$  versus  $99 \pm 19$  beats per minute.  $LVEDP_{tm}$  and  $LVESP$  were also unchanged between studies. In the emphysema group,  $LVESP$  measured  $135 \pm 10$  mm Hg at the baseline study versus  $135 \pm 24$  mm Hg at the post-1-year study, whereas corresponding  $LVEDP_{tm}$  were  $16.6 \pm 5.3$  versus  $18.8 \pm 4.6$  mm Hg. In the control group,  $LVESP$  measured  $129 \pm 15.6$  mm Hg at the baseline study versus  $138 \pm 23$  mm Hg at the post-1-year study, and corresponding  $LVEDP_{tm}$  were  $15.9 \pm 7.8$  versus  $15.1 \pm 5.3$  mm Hg.

In the chronic emphysema study, there was a distinct change in the LV diastolic pressure-dimension relation in the emphysema dog at the post-1-year study. In Figure 1, results in an emphysema dog are shown that typify the important changes found. Three findings should be noted. First, at the post-1-year study, the diastolic pressure-dimension relation obtained at low transmural pressures appeared much less compliant compared with the baseline condition. This was a consistent finding along the SL and AP axes. Second, compared with preemphysema measurements, at high  $LVEDP_{tm}$ ,

$LVEDD$  obtained along all dimensions were about the same or slightly larger after emphysema. Third, the dimensional intercept ( $D_0$ =dimension at  $LVEDP_{tm}=0$ ) obtained at the post-1-year study was not decreased along the SL axis and was consistently increased along the AP axis compared with baseline. These findings, moreover, could not be attributed to the effects of time or surgery, because they were not observed in the control dogs (see lower panel of Figure 1).

LV diastolic stiffness along the three axes was analyzed in terms of pressure-strain behavior. For a given LV diastolic pressure, Lagrangian strain ( $E$ ) represents the fractional extension from the unstressed dimension. LV pressure-strain relations for an emphysema dog are shown in Figure 2 (upper panel), and those for a control dog are shown in the lower panel. In the emphysema dog, the pressure-strain relations were shifted upward and to the left along the AP and SL axes; these findings were observed in all dogs. Along the AB dimension, the pressure-strain relation was increased in two dogs, whereas no changes were observed in the others. In the emphysema group, the reduced strain along the AP and SL axes indicates that at the post-1-year study, diastolic stiffness was increased along these axes compared with the baseline study. The mean results, given in Figure 3, show that strain decreased by about 50% over the 1-year period at the three pressures analyzed in the emphysema group. In the control group, there was no change in strain between studies.

In terms of the Kelvin elastic equation, moreover, the constant  $b$  denotes the rate of change of strain per unit change in  $LVEDP_{tm}$ . The more linear shape of the pressure-strain relation at the post-1-year study would



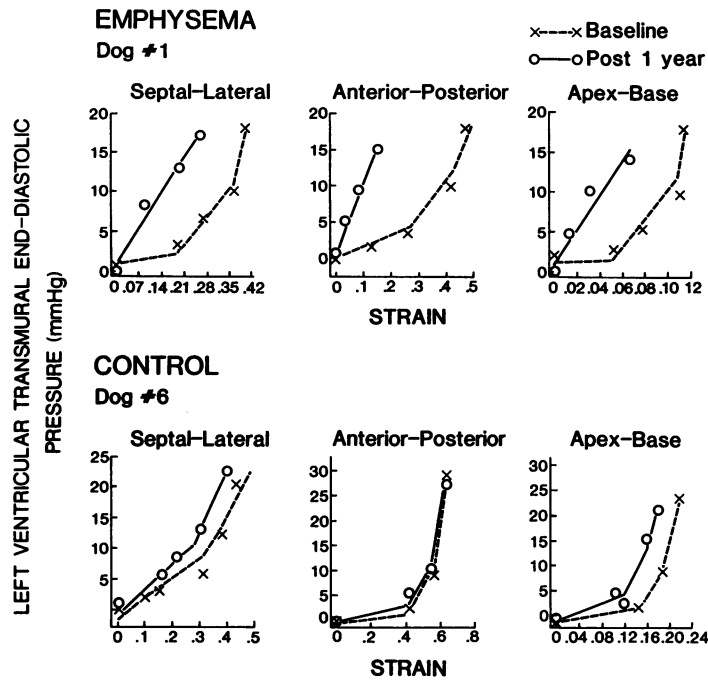


FIGURE 2. Upper panel: Graphs showing left ventricular transmural end-diastolic pressure-strain relations for an emphysema dog. At the post-1-year study, for a given transmural end-diastolic pressure, strain was reduced along the septal-lateral and anterior-posterior axes compared with baseline in all dogs, whereas strain along the apex-base axis showed inconsistent changes (see text for discussion). Lower panel: Graphs showing left ventricular transmural end-diastolic pressure plotted against strain for a dog in the control group. There were no systematic differences between baseline and post-1-year strains along the three axes in control dogs.

indicate a reduction in  $b$  compared with the baseline study. Along the AP axis, this reduction was observed in all emphysema dogs ( $6.34 \pm 3.1$  to  $4.09 \pm 4.23$ ), and along

the SL axis, it was observed in four of five emphysema dogs. No such changes were noted in the control dogs. In the emphysema dogs, furthermore, the coefficient of

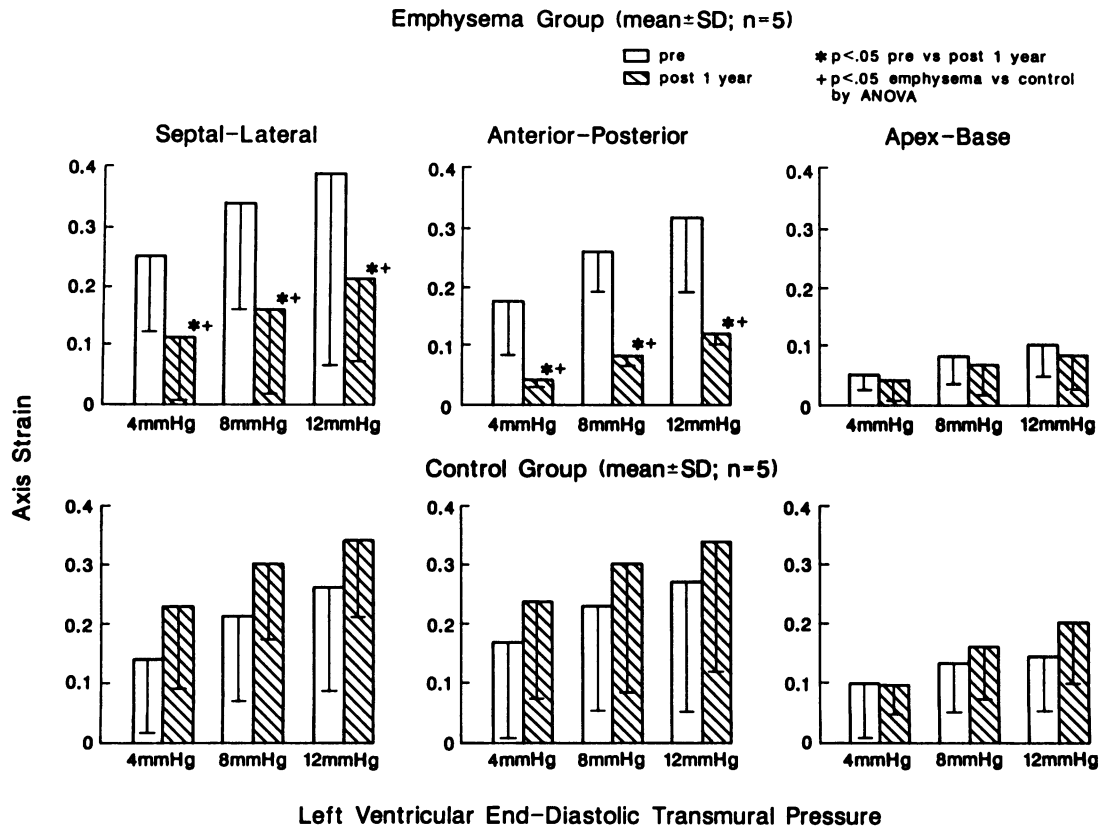


FIGURE 3. Bar graphs showing mean ( $\pm$ SD) strains at different left ventricular transmural end-diastolic pressures ( $LVEDP_{im}$ ) along the three axes for the emphysema and control groups. There was a significant decrease in strain in the emphysema group at the post-1-year study at all levels of  $LVEDP_{im}$  (\* $p<0.05$  baseline vs. post-1-year by two-way ANOVA repeated measures; + $p<0.05$  emphysema vs. control group by two-way ANOVA split-plot design in which the changes in strain at the three levels of  $LVEDP_{im}$  between baseline and post-1-year were compared in the two groups).

**TABLE 1. Midwall Circumferential Strain in the Chronic Emphysema Study**

	$\sigma = 15$ dynes $\times 10^3/\text{cm}^2$	$\sigma = 20$ dynes $\times 10^3/\text{cm}^2$	$\sigma = 25$ dynes $\times 10^3/\text{cm}^2$
Emphysema group			
Baseline	$0.11 \pm 0.05$	$0.13 \pm 0.05$	$0.15 \pm 0.063$
After 1 year	$0.050 \pm 0.037^* \dagger$	$0.062 \pm 0.039^* \dagger$	$0.071 \pm 0.039^* \dagger$
Control group			
Baseline	$0.092 \pm 0.032$	$0.11 \pm 0.033$	$0.11 \pm 0.033$
After 1 year	$0.11 \pm 0.065$	$0.12 \pm 0.062$	$0.13 \pm 0.060$

$\sigma$ , Stress. Values are mean  $\pm$  SD.

\* $p < 0.05$  baseline vs. after 1 year by two-way ANOVA repeated measures.

$\dagger p < 0.05$  control group vs. emphysema group by two-way ANOVA (split-plot design) in which the changes in strain at the three levels of stress between baseline and after 1 year were compared in the two groups.

determination (i.e., square of the correlation coefficient,  $R^2$ ) for the curve fit (before versus after emphysema) along those axes in which strain decreased between studies in the emphysema group was high:  $0.985 \pm 0.021$  versus  $0.96 \pm 0.06$  along the AP axis and  $0.97 \pm 0.03$  versus  $0.91 \pm 0.065$  along the SL axis. Similar high  $R^2$  were found for the control group.

In the chronic emphysema study, to examine the intrinsic stiffness of the LV myocardium, the relation between average midwall circumferential wall stress ( $\sigma$ ) and midwall circumferential strain was used as an approximation. The results in Table 1 show that midwall circumferential strain was decreased at the post-1-year study in the emphysema group. The  $R^2$  for the curve fit was similar to that found for the pressure-strain data.

The unstressed dimension of the LV ( $D_0$ ) along the three axes was obtained at  $\text{LVEDP}_{\text{tm}} = 0$ . In the emphysema group, rather than becoming smaller at the post-1-year study,  $D_0$  increased in four of five dogs along the SL dimension and in all dogs along the AP axis (see Table 2). Along the AB axis in the emphysema group, the changes in  $D_0$  were inconsistent. Control dogs showed no changes in  $D_0$  between the two study periods. The relative changes in unstressed end-diastolic volume between baseline and post-1-year study were estimated from the three dimensions for the two groups in which

**TABLE 2. Unstressed End-Diastolic Dimensions in the Chronic Emphysema Study**

	Baseline (mm)	After 1 year (mm)
Emphysema group		
Septal-lateral dimension	$32.3 \pm 6.2$	$36.1 \pm 6.5$
Anterior-posterior dimension	$32 \pm 4.9$	$38.2 \pm 5.2^* \dagger$
Apex-base dimension ( $n=4$ )	$49.7 \pm 2.8$	$50.8 \pm 1.4$
Control group		
Septal-lateral dimension	$32.9 \pm 6.6$	$33.3 \pm 6.3$
Anterior-posterior dimension	$34.5 \pm 12.4$	$34.9 \pm 13$
Apex-base dimension ( $n=4$ )	$47.6 \pm 8.5$	$48.8 \pm 8.6$

Dimensions measured at zero transmural left ventricular end-diastolic pressure.

\* $p < 0.01$  baseline vs. after 1 year by paired  $t$  test.

$\dagger p < 0.02$  emphysema vs. control in which changes between studies were compared between groups by two-way ANOVA split-plot design.

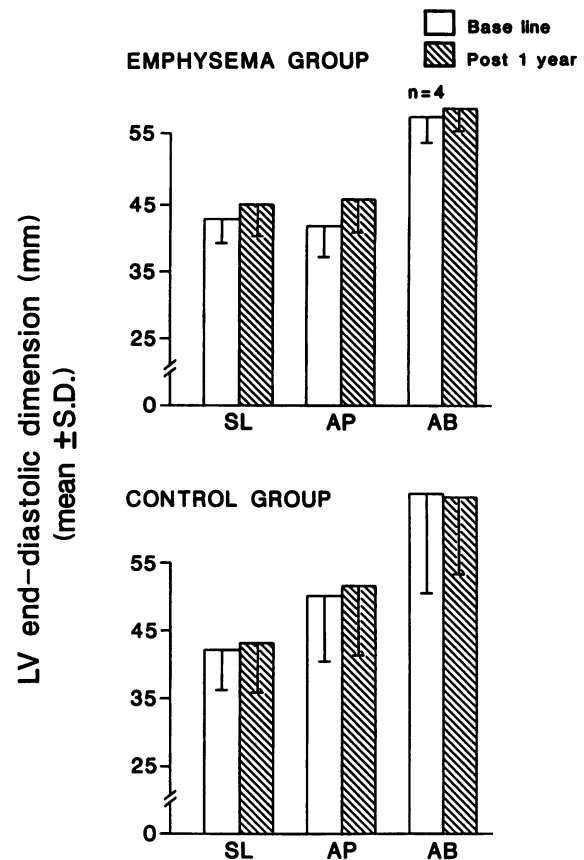


FIGURE 4. Bar graphs showing that mean ( $\pm$ SD) left ventricular (LV) end-diastolic dimensions along the septal-lateral (SL), anterior-posterior (AP), and apex-base (AB) axes were unchanged between the baseline and post-1-year studies in the emphysema and control groups for similar transmural end-diastolic pressures in the two studies.

unstressed volume was estimated from  $G \times D_{0AP} \times D_{0SL} \times D_{0AB}$  obtained at the post-1-year study divided by  $G \times D_{0AP} \times D_{0SL} \times D_{0AB}$  obtained at baseline, where  $G$  is a geometric constant (see "Discussion"). The relative increase in unstressed volume between studies in the emphysema group ( $1.36 \pm 0.53$ ) was significantly higher than in the control group ( $1.04 \pm 0.149$ ,  $p < 0.05$ ).

In the chronic emphysema study, LVEDD obtained at the baseline and post-1-year studies in the emphysema and control groups are shown in Figure 4. In the emphysema group, LVEDD (baseline versus post-1-year) were obtained at  $\text{LVEDP}_{\text{tm}}$  of  $16.6 \pm 5.3$  and  $18.8 \pm 4.6$  mm Hg, respectively; in the control group, LVEDD were obtained at  $\text{LVEDP}_{\text{tm}}$  of  $15.9 \pm 7.8$  and  $15.1 \pm 5.3$  mm Hg, respectively. In the emphysema group, compared with the baseline study, LVEDD were unchanged along the three axes at the post-1-year study. If anything, the trend was for LVEDD to increase along the AP and SL axes at the post-1-year study. Thus, after 1 year of emphysema, the LV became stiffer but not necessarily smaller, and the unstressed dimension  $D_0$  increased along the AP and SL axes.

Additional studies were performed in these emphysema dogs to examine whether errors were introduced when measurements were obtained in the closed-chest preparation in which the pericardium was relatively



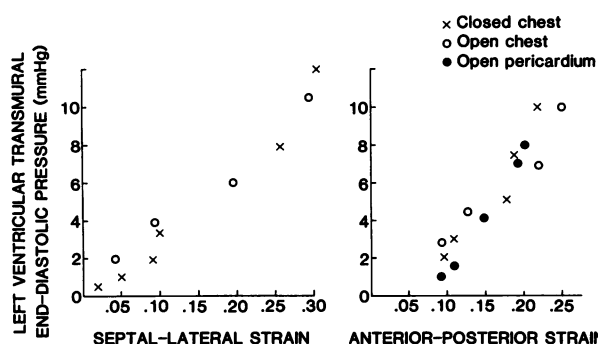


FIGURE 5. Graphs comparing left ventricular transmural end-diastolic pressure-strain relations in the closed-chest, open-chest, and open-pericardium preparations in the emphysema group. There were no differences between the three preparations used.

open but not completely removed (component 2). In three experiments in which  $D_0$  was compared in closed-versus open-chest emphysematous dogs, there was no change along the SL axis ( $4.46 \pm 3.1$  versus  $4.57 \pm 0.35$  cm) or AP axis ( $4.89 \pm 1.05$  versus  $4.9 \pm 1.0$  cm). LV pressure-strain relations were also compared in the closed- versus open-chest preparations with the pericardium removed. There were no differences between the various conditions. Two examples are shown in Figure 5. In the left panel, pressure-strain relations along the SL axis show no change in the open- versus closed-chest preparation; in the right panel, the results in closed-chest, open-chest, and open-pericardium preparations are unchanged between conditions.

In five emphysema dogs, radionuclear angiograms (component 3) were obtained to provide further evidence about whether a right to left ventricular shift was present after 1 year of emphysema. An example is shown in Figure 6. Consistent with the results obtained with sonomicrometry, after 1 year of emphysema (right-hand panel), a leftward shift in the ventricular septum was not apparent, and no consistent change in LV geometry was observed compared with the initial study (left panel). LV end-diastolic volume after 1 year of emphysema and at the initial study were  $50 \pm 22$  and

$48.3 \pm 6.9$  ml, respectively, whereas the corresponding LVEDP were  $7.0 \pm 2.4$  and  $9.3 \pm 5.4$  mm Hg. LV eccentricity index was also used to quantify whether a leftward shift in the ventricular septum occurred during end diastole or end ejection between the baseline and post-1-year studies in the emphysema group. If this ratio (defined by the AP dimension/SL dimension) increased in the emphysema group at the post-1-year study compared with the baseline study, then this would be in favor of a shift in the septum toward the LV at the post-1-year study. In the emphysema group, there was no change in this ratio at end diastole or end ejection. At end diastole, the mean  $\pm$  SD values at the baseline and post-1-year studies were  $1.00 \pm 0.09$  and  $1.02 \pm 0.15$ , respectively. At end ejection, the corresponding mean values were  $0.95 \pm 0.1$  and  $0.96 \pm 0.08$ .

Papain was given intravascularly in five separate control dogs (component 4) to see whether the changes in LV diastolic function observed after 1 year of emphysema could be directly ascribed to the effect of this enzyme on the heart. LV diastolic function was examined about 1 year after the last dose of papain was given. In contrast to the emphysema group, there were no changes in  $D_0$  in these animals. Along the SL axis,  $D_0$  measured  $3.2 \pm 0.4$  cm before papain versus  $3.1 \pm 0.7$  cm after papain; along the AP axis,  $D_0$  measured  $4.1 \pm 0.65$  cm before papain versus  $3.9 \pm 0.64$  cm after papain; and along the AB axis,  $D_0$  measured  $6.0 \pm 0.9$  cm before papain versus  $6.0 \pm 0.8$  cm after papain. Moreover, strains measured along the three axes at LVEDP<sub>im</sub> of 4, 8, and 12 mm Hg were not decreased in this group. The before versus after papain strains obtained at the respective pressures along the SL axis were  $0.11 \pm 0.02$  versus  $0.15 \pm 0.07$ ,  $0.16 \pm 0.08$  versus  $0.22 \pm 0.08$ , and  $0.22 \pm 0.02$  versus  $0.24 \pm 0.1$ ; along the AB axis, the respective strains were  $0.072 \pm 0.02$  versus  $0.13 \pm 0.03$ ,  $0.14 \pm 0.03$  versus  $0.19 \pm 0.034$ , and  $0.18 \pm 0.03$  versus  $0.22 \pm 0.035$ ; and along the AP axis, the respective strains were  $0.14 \pm 0.01$  versus  $0.23 \pm 0.05$ ,  $0.23 \pm 0.04$  versus  $0.28 \pm 0.07$ , and  $0.29 \pm 0.05$  versus  $0.32 \pm 0.1$ .

The effect of acute pulmonary hypertension on LV diastolic function (component 5) was examined in another group of control animals ( $n=5$ ) in which the analysis was the same as in the chronic emphysema

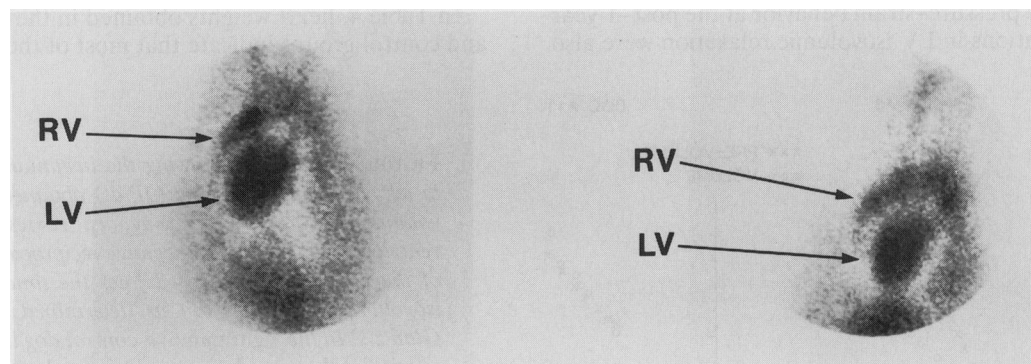


FIGURE 6. Gated radionuclide angiograms performed at intervals similar to those in the sonomicrometry experiments. During diastole, a right to left shift in the ventricular septum after emphysema (right panel) did not appear to alter left ventricular (LV) diastolic mechanical properties compared with the initial study (left panel). Note, also, that although this view was obtained in the left anterior oblique position, in which the right and left ventricles in the canine heart could be maximally separated, in terms of human radionuclide angiograms, this view appears more representative of the left lateral position, since the canine heart is oriented in a slightly different manner than the human heart. RV, right ventricle.

**TABLE 3. Lagrangian Strain in Acute Right Ventricular Pressure Overload Study**

	Baseline	Pulmonary hypertension
Anterior-posterior strain		
LVEDP <sub>tm</sub> =4	0.088±0.025	0.09±0.07
LVEDP <sub>tm</sub> =12	0.24±0.10	0.23±0.09
Septal-lateral strain		
LVEDP <sub>tm</sub> =4	0.18±0.21	0.19±0.21
LVEDP <sub>tm</sub> =12	0.41±0.47	0.35±0.35

LVEDP<sub>tm</sub>, left ventricular transmural end-diastolic pressure. Values are mean±SD.

study. In the acute pulmonary hypertension study, mean RVPSP<sub>tm</sub> averaged 23.8±6.7 mm Hg at baseline and after occlusion increased to 33.5±7.9 mm Hg ( $p<0.05$ ). Corresponding increases in RVEDP<sub>tm</sub> were from 5±1.4 to 8.3±2 mm Hg ( $p<0.05$ ). LVEDP<sub>tm</sub> was unchanged between conditions and averaged 14.8±4 versus 15.1±3.5 mm Hg, respectively. Thus, the cardiac pressures produced in this acute study were similar to those found in the chronic emphysema study.

In contrast to the chronic emphysema study, in which the SL dimension did not change between the baseline and post-1-year studies, the results obtained in the acute hypertension study showed that SL end-diastolic dimensions decreased during occlusion in all the dogs examined, from 32.8±6.4 mm at baseline to 31.6±8 mm after occlusion. Moreover, the unstressed dimension along the SL axis (i.e.,  $D_0$ ) also decreased during occlusion from 26.4±10 to 25.0±5.9 mm,  $p<0.05$ . Since  $D$  and  $D_0$  decreased to about the same extent during occlusion, strain was nonsystematically decreased along this axis, although a tendency for a decrease was present at an LVEDP<sub>tm</sub> of 12 mm Hg (see Table 3). Along the AP axis, dimensions  $D$  and  $D_0$  did not change between before and after occlusion ( $D=5.04±0.64$  versus  $5.05±0.65$  cm at LVEDP<sub>tm</sub>;  $D_0=4.16±0.59$  versus  $4.16±0.59$  cm). In the acute hypertension study, therefore, no increases in  $D_0$  were found along the SL and AP axes during occlusion, and along the AP axis, strain did not change between conditions (see Table 3).

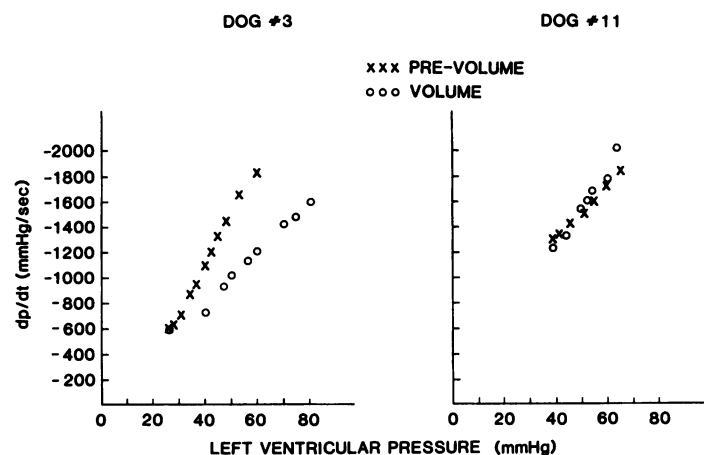
In the emphysema group, in addition to changes in LV diastolic pressure-strain behavior at the post-1-year study, alterations in LV isovolumic relaxation were also

observed in response to volume expansion and phenylephrine infusion. At the post-1-year study, the pre-volume expansion  $T$  was not different between the emphysema ( $n=9$ ; 29.3±13 msec) and control ( $n=10$ ; 30.9±9.5 msec) groups. However, when volume was infused to increase preload (6% hetastarch in normal saline solution, 20 cm<sup>3</sup>/kg), there was a significant slowing of relaxation in the emphysema group that was not observed in the control group. An example is shown in Figure 7. The right panel shows a control dog. Consistent with the findings of Karliner et al,<sup>22</sup> the relation of  $dP/dt$  to ventricular pressure was the same before and after volume expansion. The left panel shows an emphysema dog. At the post-1-year study, the slope of the relation shifts downward and to the right compared with before volume expansion, and  $T$  is increased. There was a significant increase in  $T$  in response to volume expansion in the emphysema group compared with pre-volume expansion measurements (29.3±13 to 36±17 msec,  $p<0.05$ ). This response was different from that observed in the control group, in which  $T$  did not change with volume infusion (30.9±9.5 versus 29.7±6 msec;  $p<0.01$  between groups). There was no difference in LVESP, LVEDP<sub>tm</sub>, or heart rates between groups during these measurements to change  $T$  (see above).

In five control and emphysema dogs, the  $T$  obtained during phenylephrine infusion was also measured at the baseline and post-1-year studies. In the emphysema group, LVESP obtained during phenylephrine infusion was not different between studies and averaged 196±30 mm Hg at baseline and 204±31 mm Hg at the post-1-year study; LVEDP<sub>tm</sub> were also not different and measured 27±11 and 30±6.2 mm Hg, respectively. In the control group, the corresponding LVESP were 198±9 and 214±24 mm Hg, and the corresponding LVEDP<sub>tm</sub> were 31±10 and 32.9±10 mm Hg. Figure 8 shows an increase in  $T$  in all dogs with emphysema between the baseline and post-1-year studies;  $T$  in the control dogs did not change.

In the five animals given intravenous papain,  $T$  did not increase in response to volume infusion (35.8±12 versus 28±18 msec) at the post-1-year study or show an increase in  $T$  in response to phenylephrine infusion between studies (40±26 versus 24±4 msec).

In Table 4, heart weights obtained in the emphysema and control groups indicate that most of the increase in



**FIGURE 7.** Graphs showing the instantaneous change in left ventricular pressure ( $dP/dt$ ) obtained during isovolumic relaxation plotted against corresponding left ventricular pressure. The negative reciprocal of the slope of the relation ( $-1/\text{slope}$ ) defines the time constant of isovolumic relaxation ( $T$ ) as determined by Raff and Glantz.<sup>12</sup> In the right panel, a control dog is shown. The relation is the same before and after volume infusion. In the left panel, an emphysema dog is shown. With volume expansion, the slope shifts downward and to the right and the time constant increases in the emphysema dog (see text for discussion).

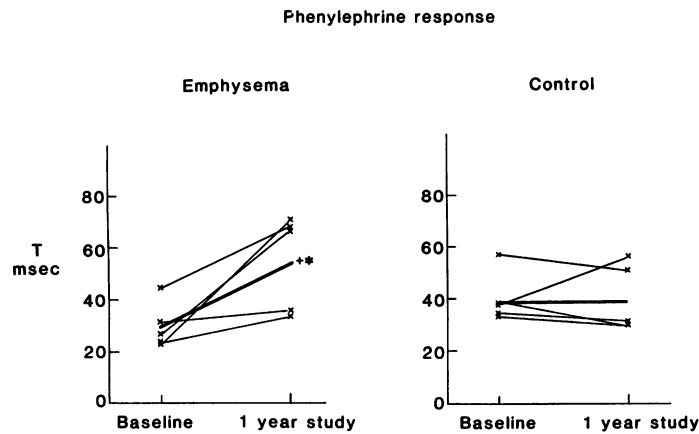


FIGURE 8. Graphs showing the time constant of isovolumic relaxation ( $T$ ) obtained during phenylephrine infusion plotted on the ordinate for the individual emphysema dogs (left panel) and control dogs (right panel) at the baseline and post-1-year studies. Thick lines in the respective panels are the mean values. In the emphysema dogs, there was a significant increase in  $T$  at the 1-year study compared with baseline ( $*p < 0.05$  by paired  $t$  test). The increase in  $T$  between baseline and post-1-year study in the emphysema dogs was significantly different from the change in  $T$  over this interval in the control dogs ( $+p < 0.05$  by two-way ANOVA split plot). See text for discussion.

weight occurred in the area of the RV and intraventricular septum. The results showed similar findings when expressed relative to body weight. Average wall thickness was just slightly increased in the emphysema group ( $1.38 \pm 0.138$  versus  $1.21 \pm 0.23$  cm) but was not significantly different between groups.

In the emphysema and control groups, arterial blood gases were obtained with the animals anesthetized and ventilated. Arterial  $PO_2$  showed a slight decrease in the emphysema group from baseline to the post-1-year study ( $94 \pm 4.2$  versus  $81 \pm 8.4$  mm Hg;  $p < 0.01$ ). There was no change in  $PO_2$  in the control group ( $93 \pm 4$  versus  $95 \pm 3$  mm Hg;  $p < 0.01$  between groups).  $PCO_2$  and pH in the emphysema group (baseline versus post-1-year study,  $38 \pm 2$  versus  $32 \pm 2$  mm Hg and  $7.37 \pm 0.03$  versus  $7.38 \pm 0.02$ , respectively) were not different between studies or between groups (control group,  $36 \pm 2$  versus  $35 \pm 3$  mm Hg and  $7.36 \pm 0.03$  versus  $7.36 \pm 0.02$ ).

### Discussion

Changes in LV diastolic function were observed in the emphysema group over the 1-year interval of the study. At the post-1-year study, LV diastolic function was altered such that the ventricle along the AP and SL axes became stiffer without a reduction in chamber dimensions. LV diastolic pressure-strain and midwall circumferential stress-strain relations were decreased compared with the baseline study (see Table 1 and Figures 1–4). Altered LV isovolumic relaxation was also observed at the post-1-year study in the emphysema group. In the emphysema group,  $T$  increased in response to volume infusion and to phenylephrine infusion compared with the baseline study and compared with the control group. These findings in the emphysema group, moreover, were different from those observed in a model of acute pulmonary hypertension in which a similar preparation was used. In the acute pulmonary hypertension study, the elevation in RVPSP was similar to that produced in the chronic study, yet

the changes in LV diastolic function were markedly different in the two studies (see Table 3).

Thus, the findings observed in the chronic emphysema study considered in conjunction with those in the additional studies support the contention that pulmonary hypertension in this model of emphysema results in altered LV mechanics that cannot be ascribed simply to right to left ventricular septal shift. Furthermore, the findings in our emphysema model cannot be attributed to the effects of time or surgery, because the control group in the chronic emphysema study showed no changes in LV diastolic mechanics between the baseline and post-1-year studies.

### Influence of Chronic Emphysema on LV Chamber Size

In the emphysema group, the LV diastolic findings observed at the post-1-year study were very similar to those reported by Laks et al,<sup>4</sup> who used a model of pulmonary artery banding to increase RVPSP to a range between 45 and 90 mm Hg. They found that in the pulmonary artery-banded group, LV volume at zero distending pressure was increased compared with a control group ( $40.5 \pm 2.5$  versus  $23.1 \pm 1.6$  ml/m<sup>2</sup> body surface area) after 2–40 weeks of banding. In the present study, similar results were observed in the chronic emphysema study. In the emphysema group, at the post-1-year study, we found that  $D_0$  was significantly increased along the AP dimension, tended to be increased along the SL dimension, and was unchanged along the AB dimension (see Table 2). As an approximation, unstressed volume ( $V_0$ ) can be calculated from  $V_0 = GD_{0AP}D_{0SL}D_{0AB}$ , where the geometric constant  $G = \pi/6$  and is considered unchanged between the baseline and post-1-year studies.<sup>9,10,15</sup> Then from Table 2,  $V_0$  in the emphysema group averaged 26.6 cm<sup>3</sup> during baseline and 36.2 cm<sup>3</sup> at the post-1-year study; thus, after 1 year of pulmonary hypertension, LV dilation occurred at zero transmural pressure in the emphysema group.

TABLE 4. Heart Weights in the Chronic Emphysema Study

	RV weight (g)	Septum+LV free wall weight (g)	Septum weight (g)	LV free wall weight (g)	Body weight (kg)
Emphysema	$59.3 \pm 8.4^*$	$145 \pm 5.4^*$	$74.3 \pm 1.6^*$	$70.2 \pm 20$	$29.5 \pm 6.2$
Control	$42 \pm 1.6$	$113 \pm 11$	$53 \pm 9.2$	$60 \pm 7.4$	$27 \pm 3.6$

RV, right ventricle; LV, left ventricle. Values are mean  $\pm$  SD.

\* $p < 0.05$  between groups by unpaired  $t$  test ( $n = 4$  in each group).



On the other hand, in our acute pulmonary hypertension study (component 5), compared with preocclusion,  $D_0$  did not increase along the AP axis and decreased along the SL axis during occlusion. These results are similar to those usually reported in models of acute pulmonary hypertension in which ventricular interdependence effects have been shown to decrease LV diastolic volume at most transmural pressures.<sup>10</sup> Thus, the findings observed in the emphysema group were distinctly different from those in the acute pulmonary hypertension study and cannot be attributed to the preparation used.

The mechanism by which pulmonary artery banding may cause LV hypertrophy, increased  $V_0$ , and altered material properties is not clear. Laks et al<sup>4</sup> suggested that since the RV and LV myocardium may behave as a single structure, sustained stress to one could result in hypertrophy and dilation of both. Alternatively, overloading of the RV results in the release of a substance that reaches the LV and causes hypertrophy and dilation. In terms of the mechanism, anatomic changes in the LV induced by pulmonary hypertension could cause chamber enlargement. Laks and coworkers<sup>5</sup> have shown that with pulmonary hypertension, mean widths of LV intercalated disks and cell lengths could increase compared with the normal condition to cause LV dilation.

However, some investigators have shown that because of chronic RV pressure overload, LV volume would decrease for a given distending pressure compared with the normal situation.<sup>10</sup> Differences between studies may be resolved by the findings of Laks et al,<sup>4</sup> in that the latter investigators observed that LV volume correlated negatively with the duration of pulmonary artery banding and the degree of pulmonary hypertension. They postulated that an increase in RV wall tension that results from increased pulmonary afterload causes an initial dilation of the LV and, if sustained, results in an increase in LV mass that may be generalized and eventually lead to a decrease in LV volume.

In terms of the concepts of Laks et al,<sup>4</sup> relative LV dilation would be expected in our model, because the pulmonary hypertension in emphysema is relatively mild and because it occurs very gradually. Indeed, the RVPSP obtained in the present study were just at the lower range of those in the study of Laks et al. In other models of pulmonary hypertension, however, such as pulmonary artery banding, pulmonary hypertension is acutely increased and the RV pressures are much higher than in this emphysema model.<sup>10</sup> The changes in LV function that occur in the two situations may be different, because the time courses of the stresses on the ventricles are different. In clinical medicine, changes in heart function induced by pulmonary emphysema would occur gradually over a considerable period of time. Thus, compared with other models, the changes observed in LV mechanics in our model may be more representative of the changes that occur in clinical emphysema.

#### *Effect of Chronic Emphysema on LV Chamber and Myocardial Stiffness*

In the chronic emphysema study, LV diastolic pressure-strain relations were used to assess elastic restraints to diastolic filling. They cannot be used to examine changes in the intrinsic muscle properties of the LV myocardium because they do not account for the

effect of external constraints to LV filling or for changes in geometry of the LV chamber. Our ultrasonic crystal and radionuclide angiography results (component 3) did not show a change in LV geometry between baseline and post-1-year studies in the chronic emphysema study. Compared with the control group, the LV pressure-strain relations along the SL and AP dimensions were less compliant to extension from unstressed dimension in the emphysema group. Thus, LV chamber stiffness increased along these axes after 1 year of emphysema. This pressure-strain analysis, moreover, is analogous to the calculation of specific compliance (i.e.,  $\Delta \text{volume} \cdot \Delta \text{pressure}^{-1} \cdot \text{unstressed dimension}^{-1}$ ). Laks et al<sup>4</sup> did not calculate specific compliance of the LV per se in their study but from the results given in their Table 2, specific compliance in their pulmonary artery-banded dogs decreased about 25% compared with their control group. In the present study, we found that LV diastolic strain decreased a slightly greater amount, about 50% in the emphysema group (see Figure 3).

To examine the intrinsic stiffness of the LV myocardium in an equatorial hoop of the LV, the relation between midwall circumferential stress and strain was constructed. The calculation of stress in this analysis normalizes forces in the LV wall both for external constraints and for LV geometry. We incorporated both pleural and RV pressures into the determination of effective external pressure for the calculation of this wall stress. The decrease in strain in the emphysema group (see Table 1) suggests that the intrinsic compliance of the LV has been altered. However, the analysis does not indicate whether the changes in intrinsic stiffness occurred in the region of the interventricular septum or the septal free wall.

It is important to note, however, that this analysis should be taken only as an approximation. Many assumptions were made in its derivation, and different equations may have also been used.<sup>17</sup> In the present study, an average wall thickness value  $h$  was used in the calculation of wall stress. In the emphysema group, regional changes in the LV myocardium may have occurred, since changes in heart weight along the septum in the emphysema group appeared greater than along the free wall (see Table 4). Indeed, because of our concern about asymmetric changes in LV hypertrophy between baseline and post-1-year study, it was impractical to measure changes in wall thickness in which crystals were placed in one specific area. There was no way to predict exactly where changes would occur. The same difficulty would occur with respect to pathological sampling. At autopsy, there was no region where wall thickness was clearly increased in the emphysema group, although changes in the ventricular septum again appeared to be greater than in other regions. Our results are therefore similar to those observed in the study of Laks et al,<sup>4</sup> in which wall thickness was not increased when pulmonary artery banding was mild and of short duration.

Additional factors to consider with regard to our analysis of wall stress is that wall thickness may vary as a function of coronary perfusion pressure, which is a much more important determinant of thickness than coronary flow.<sup>23</sup> Wall thickness increases with high coronary perfusion pressures and decreases at low pressures. However, over a range of coronary perfusion

pressure between 100 and 50 mm Hg, which was found during occlusion of the vena cava, changes in wall thickness would be trivial. Gaasch et al<sup>23</sup> found the decrease to be around 0.2 mm over this pressure range. Thus, wall thickness changes would not be a limiting factor in interpretation of the pressure-strain data in Figures 2 and 3. On the other hand, by necessity, average wall thickness was used to calculate the stress-strain data (see Table 1), and these values were obtained at autopsy, since there was no other way to acquire the data. Still, Gaasch et al<sup>23</sup> found wall thickness to decrease by only 0.5 mm, from 11.2 to 10.7 mm, when coronary perfusion pressure fell from 100 to 0 mm Hg in similar-size dogs. Changes in wall thickness resulting from the effect of coronary perfusion pressure would therefore be relatively small (4%) compared with the contribution of cardiac muscle. In the present study, since LV systolic and diastolic pressures were similar in the two groups, these findings would suggest a similar quantitative effect of coronary perfusion pressure on wall thickness in both groups. However, because of the limitations of the assumptions needed to measure wall stress, it is acknowledged that the stress-strain analysis in Table 1 can be used only as an approximation.

#### *Changes in LV Relaxation in Chronic Emphysema*

At the post-1-year study, LV isovolumic relaxation was also altered in the emphysema group. LV relaxation is an active energy-dependent process. The factors that influence the relaxation process are multifactorial and controversial. Heart rate, loading conditions, contractile state, and uniformity of the relaxation process may all affect the time constant.<sup>11,12,22,24,25</sup> Using a similar canine preparation, Che-Ping et al<sup>24</sup> have shown that augmented preload by dextran infusion does not alter T. In our control group, T was unchanged before and after volume infusion. Unlike the control group, however, T increased with volume infusion in the emphysema group and also increased from the baseline to post-1-year studies during phenylephrine infusion, despite the fact that preload, afterload, and heart rates were unchanged between studies. Because of the multiple factors that determine T, it is not possible to assess which one was responsible for the increases in T observed in the emphysema group. Thus, our study points out that changes in T may occur in emphysema, but it does not denote the mechanism.

Although T increased in the emphysema group, the prolongations in T were small. According to Weiss et al,<sup>13</sup> if the onset of ventricular relaxation (i.e., maximum negative dP/dt) to the beginning of the next systole is <3.5 time constants, then the next systole could occur before relaxation was completed. In the present study, the interval between isovolumic relaxation and the start of the next systole was >3.5 T during any intervention. It appears unlikely, therefore, that these small increases in T contributed to altered LV end-diastolic pressure-dimension relations at the post-1-year study in the emphysema group.

In clinical medicine, the status of LV function in emphysema has been controversial, and findings of both normal and abnormal function have been reported. In COPD patients, Baum et al<sup>2</sup> found that the LV was dilated and that the relation of stroke volume to LVEDP was depressed compared with normal subjects.

Although controversial, LV hypertrophy and dilation have variably been found at autopsy in emphysema patients.<sup>26,27</sup> Because of the variable nature of lung disease in patients with COPD, as well as the length of time to develop illness, it has been difficult to delineate the precise changes in LV mechanics that occur in this disease. Whereas models of pulmonary artery banding have been useful, pulmonary hypertension is abruptly increased in these models, and thus the time course of the increase in pulmonary afterload does not accurately reflect the condition in humans. Our model mimics the clinical condition more closely than other models do.

In the present study, our results show that LV diastolic stiffness increased along the anterior-posterior and septal-lateral axes after 1 year of emphysema. Our results do not clarify whether the changes in LV diastolic function observed were caused by global changes in the LV myocardium as suggested by Laks et al,<sup>4</sup> but this seems the most likely mechanism. This mechanism could lead to additional changes in LV geometry that in turn may further alter LV stiffness in emphysema. Moreover, our results do not exclude ventricular interdependence as an important mechanism of altered LV diastolic performance in COPD in the clinical condition. In the present study, we purposely used a relatively open pericardial preparation to minimize any effect of ventricular interdependence on LV mechanical properties in emphysema. However, a limitation of the study is that it may not be totally possible to exclude this effect from contributing to our results. Whereas the problems of applying animal models to human disease are clearly recognized, this study suggests that mechanisms other than ventricular interdependence may lead to a decrease in LV diastolic compliance in COPD.

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## Altered left ventricular chamber stiffness and isovolumic relaxation in dogs with chronic pulmonary hypertension caused by emphysema.

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