Left Ventricular Filling and Diastolic Pressure-Volume Relations in the Conscious Dog


ABSTRACT

In 7 conscious dogs, left ventricular diastolic volume (V) was estimated by taking biplane cineradiographs with the left ventricular cavity previously outlined by permanent radiopaque markers. Left ventricular pressure (P) was measured with an implanted miniature transducer. There were two rapid filling periods during early and late diastole; little filling occurred during the middle third of diastole (diastasis). The diastolic pressure-volume relationship was approximately exponential and was fitted by the equation \[ P = -a + be^{ct}, \]

where \(a\), \(b\), and \(c\) are positive constants; the relationship appeared to be determined principally by the elastic properties. The effects of infusions of saline, isoproterenol, calcium gluconate, and methoxamine suggested that viscous and inertial properties are also important determinants of diastolic left ventricular mechanics. No significant series viscosity was observed. Plastic properties were not detected. The elastic properties were not affected by agents having a positive inotropic effect. End-diastolic pressure often differed from that predicted by the exponential equation above, suggesting that it is not a reliable index of end-diastolic volume and left ventricular compliance.

ADDITIONAL KEY WORDS tantalum markers biplane cineradiography end-diastolic pressure left ventricular compliance isoproterenol elastic components myocardial plasticity series viscous element inertial properties left ventricular distensibility calcium methoxamine

The present study was undertaken to answer the following questions in the conscious dogs: (a) how does the volume of the left ventricle change during diastole; (b) what is the relationship between left ventricular pressure and volume during diastole; (c) how is this relationship affected by the physical properties of the myocardium; and (d) under what circumstances might this pressure-volume relationship change? All these factors have important influences on end-diastolic volume or initial fiber length, which is in turn a major determinant of ventricular contraction (1-3).

A radiographic technique for measuring left ventricular volume was used in this study. It has two main advantages over an indicator washout technique: it is possible to measure volume throughout diastole, and it is possible to assess the accuracy of the method by checking it against known volumes of different shapes and known volumes in the post-mortem heart. To avoid anes-

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thesia, which shrinks the heart (4), and injected contrast medium, which dilates the heart and gives only a short period of opacification, we have used permanent markers (5) to outline the left ventricular cavity. Tantalum, a chemically inert and densely radiopaque metal, was employed for this purpose.

**Methods**

**INSERTION OF TANTALUM SCREWS**

Ten mongrel dogs weighing 14 to 26 kg were anesthetized with pentobarbital, a carotid artery was cannulated, and a catheter was inserted retrograde into the left ventricle under fluoroscopic control. The tip of the catheter was pushed against the wall of the cavity. A flexible wire screwdriver carrying a tantalum screw 2.0 mm by 0.9 mm made of tantalum wire 0.12 mm in diameter was then inserted through the lumen of the catheter, and twisted so that the screw was driven into the myocardium (5). The catheter was manipulated to a new position and the procedure repeated until the cavity was completely outlined in both the anteroposterior and lateral projections (Fig. 1). During the procedure, the cavity was opacified periodically with Renografin to determine whether the screws were well distributed around the entire perimeter in each projection. It was usually necessary to change the bend on the catheter to reach the anterior wall and the region of the mitral valve ring. Additional screws were inserted from the ascending aorta through the sinuses of Valsalva into the aortic valve ring. When satisfactory marking of the ventricle had been achieved (with 20 to 30 screws), the catheter was withdrawn, the wound repaired, and the dog allowed to recover. In one dog, a tantalum screw came loose during the procedure and lodged in a coronary artery causing massive infarction and death before recovery from the anesthetic. There were no ECG changes in the other dogs. Left ventricular contraction (as judged by cardiac output, peak aortic flow, maximum acceleration of blood from the left ventricle, aortic pressure, left ventric-
ESTIMATION OF LEFT VENTRICULAR VOLUME

Two 6-inch GEC image amplifiers were used to produce biplane cineradiographs on 16-mm film; the framing rate was 60/sec. The developed films were projected so that the image on the screen was 1.5 times the size it would have been on the input phosphor of the image amplifier. The screws chosen for the analysis were those which consistently marked the cavity as shown by an angiogram. Some screws were found outside the outline of the cavity; these had been driven too deep into the muscle. Others found inside the cavity were demarcating the other projection. All these screws were ignored. Ten to 20 screws were used in each projection; a few screws could be used for both projections. During the analysis when no contrast medium was present, the outline of the cavity was drawn using the chosen screws (Fig. 1, A). The drawing was made with red pencil on an IBM multiple-choice examination answer sheet, and the sheet was filled in in black as described by Goerke and Carlsson [8].

The anteroposterior and lateral views were then fed into an IBM scanner that read only the black marks on the sheet. An IBM computer (system 360, model 50) was programmed to calculate the volume (8). The program corrected for the 1.5 magnification in projection and for the magnification resulting from the diverging x-ray beams. The method for calculating volume (a modification of that of Chapman et al. [9]) divided the ventricle into a series of 10 to 18 elliptical slices 6 mm thick; these slices were "cut" perpendicular to the head to foot axis (8), which is common to both projections. The volume of each slice was calculated from the formula for a right-angled elliptical cylinder.

\[ V = \frac{\pi h a b}{4}, \]

where \( V \) is the volume of the slice, \( h \) the thickness, \( a \) the diameter of the slice in the vertical projection, and \( b \) the diameter of the horizontal projection. The total volume of the ventricle was then obtained by summing the volumes of all the slices.

SURGICAL PROCEDURES

The activity and behavior of the dogs returned completely to normal within a week after insertion of the screws. A left thoracotomy was carried out under pentobarbital anesthesia and aseptic conditions 1 week to 8 months after screw implantation. A small incision was made in the anterior wall or apex of the left ventricle. The pressure-sensitive head of a Microsystems 1017 strain gauge pressure transducer was inserted through this incision into the left ventricular cavity. It was then withdrawn until the back of the head came up against the ventricular wall. The incision was then closed with a purse string and the transducer tied to the purse string. In this manner the transducer was fixed against the inside of the left ventricular wall. A similar transducer was implanted in the ascending aorta in one dog and in the aortic arch in another. A polyvinyl catheter was inserted into the aortic arch via the left internal mammary artery in the other dogs. An appropriately sized electromagnetic flowmeter (cuff type) was implanted around the ascending aorta (except in dog Q). A polyvinyl or silastic catheter was implanted in the left atrium via the appendage. The pericardium was left open. The chest was closed with a drainage tube in place and the dog allowed to recover. The drainage tube was removed within 24 hours. Studies were carried out after full recovery from surgery (from 5 days to 4 weeks). The entire procedure of screw and transducer implantation was successful in seven dogs (Table 1).

MEASUREMENT OF PRESSURE

The pressure transducer was calibrated in vitro in a water bath at 36.5°C with a mercury column as the reference. For this purpose the transducer was mounted in a watertight fashion into an air-filled open-ended tube. The open end came above the water surface so that the transducer was exposed to atmospheric pressure for establishing zero. The tube was then connected to a mercury column for static calibration of the gauge. All pressure measurements were made relative to atmospheric pressure. Alternatively, the zero and calibration were determined in vivo by matching the transducer output to a reference pressure recorded with an external strain gauge via a catheter.
inserted retrograde into the left ventricle from a peripheral artery. The mid chest position was used as zero reference level for the external catheter manometer system (with the dog lying on its right side). The zero was also checked when the animal was killed (by pentobarbital) by opening the ventricle to the atmosphere and draining it of blood. In dog U, the 1017 gauge was incorrectly positioned within the muscle; an SF-1 catheter-tip manometer was used to measure left ventricular pressure in this dog by techniques described previously (10). There was negligible drift in this SF-1 manometer (as judged by frequent zero checks on the external gauge).

In the three dogs in which a catheter was implanted in the aorta, the mean pressure was measured with a Statham P23Dc strain gauge; no reliance can be placed on the pulsatile waveform in these experiments.

MEASUREMENT OF FLOW

Aortic flow was measured with a Statham (Medicon) M4001 or Biotronex pulsed logic electromagnetic flowmeter. They were calibrated at the end of the experiment by reopening the chest and inserting a cannulating flow transducer of known calibration into the descending aorta. All branches of the aorta between the cuff and cannulating transducers were tied off so that the two were in series. Zero was obtained by arresting the heart with acetylcholine (11). The stroke volume was calculated from the area under the flow curve of the cannulating transducer. Since both flow transducers were linear, this same stroke volume was equivalent to the area under the flow curve of the cuff transducer. Knowing the time base of the recorder, the flow calibration of the cuff transducer was then obtained.

RECORDING

Left ventricular pressure, aortic pressure, and aortic flow were recorded on an Offner type R Dynograph. The left ventricular pressure was also recorded on a second channel at high sensitivity so that the diastolic changes were displayed and the trace went off scale in systole. Left ventricular stroke volume was obtained from aortic flow using an Offner resetting integrator. A paper speed of 250 mm/sec was used during radiographic filming.

Two methods of synchronizing the films were used. (a) The first outward movement of the screws at the beginning of diastole (the most rapid movement of the cardiac cycle) was synchronized with the corresponding movement on the other projection. (b) A relay was used to switch on and off a solenoid-operated marker flag on each image amplifier. It was shown, by counting frames from these markers to the beginning of diastole, that the first method of synchronization was correct. Synchronization between the films and the Offner record was achieved with simultaneous markers.

PROTOCOLS AND ANALYSIS

The dogs were trained to lie quietly on the x-ray table on their right sides, and control recordings were made. In three dogs, one slow and one fast heart rate were obtained by right atrial pacing. Saline (300 to 800 ml of 0.9%) was immediately infused into the left atrium after a control record had been taken; the infusion rate was 50 ml/min. Further readings were then taken. Alternatively, increasing doses of isoproterenol (up to 2 μg), calcium gluconate (up to 1.0 g) or methoxamine (up to 2.0 mg) were injected. Following isoproterenol, recordings were made as soon as there was a clear-cut increase in heart rate with an increase or no change in stroke volume; maximum rate of rise of left ventricular pressure (LV dP/dt) always increased in these circumstances. Following calcium gluconate, recordings were made as soon as there was a clear cut increase in LV dP/dt max. Following methoxamine, recordings were made as soon as systolic left ventricular pres-
sure increased. This was always accompanied by considerable bradycardia. The changes with all three drugs occurred within 1 minute after the control recordings.

Diastolic filling curves were constructed by plotting pressure and volume against time every 1/60 sec (the time between frames) throughout diastole. Only beats occurring during the expiratory pause were analyzed. The diastolic pressure-volume data was fitted (least squared deviations) by an exponential curve \( P = -a + be^{t} \), where \( P = \) pressure, \( V = \) volume and \( a, b, \) and \( c \) are positive constants, using a Fortran program that weighted the high and low pressure points equally. A standard deviation of the data points from this curve was calculated from the equation

\[
S = \left( \frac{\sum (P - \bar{P})^2}{N-2} \right)^{1/2}
\]

where \( \bar{P} \) is the estimate of \( P \) from the exponential equation and \( N \) the number of data points. The correlation coefficient, \( r \), was calculated from the equation

\[
r = 1 - \frac{\sum (P - \bar{P})^2}{\sum (P - \bar{P})^2},
\]

where \( \bar{P} \) is the estimate of \( P \) from the exponential equation and \( \bar{P} \) the mean of \( P \).

It is not possible to calculate confidence limits for this nonlinear function. There is therefore no satisfactory statistical method for comparing control curves with those obtained after drug administration.

**CRITIQUE OF LEFT VENTRICULAR VOLUME MEASUREMENT**

**Reproducibility**

On six occasions within one day, a practiced observer searched the films for the same pair of frames and traced them to calculate volume. The result was 43.1 ml ± 1.42 (1 SD, 3.3%). For another dog, one practiced observer and five observers who had never before made tracings from x-rays were asked to set up the projector and trace the same pair of frames. The results for volume were 44.7 ml ± 3.08 (1 SD, 6.9%). Subsequently, all analyses (except for dog H) were done by a single observer.

This observer analyzed eight consecutive beats for end-diastolic and end-systolic volume. A steady state was present as judged by the stroke volume measured by electromagnetic flowmeter; the mean stroke volume for the eight beats was 32.8 ml ± 0.31 (1 SD) using the independent flowmeter calibration. End-diastolic volume was 55.8 ml ± 0.56 (1 SD) and end-systolic volume 24.1 ml ± 1.14 (1 SD) for the same eight beats. Stroke volume determined by subtracting end-systolic volume from end-diastolic volume was 31.8 ± 1.42 (1 SD). Some of this variability was caused by respiration; for this reason all subsequent analyses were made during the expiratory pause (see section on analysis above). A possible reason for the poorer reproducibility of end-systolic volume (and therefore radiographic stroke volume) was that the twisting motion of the heart in systole brought a somewhat different projection of the left ventricular cavity into the plane perpendicular to the x-ray beam. We have corrected for this by reploting the relationship of the screws to the cavity from the systolic phase of the angigram. However, this relationship was less constant during systole than the corresponding relationship during diastole. We do not think our method should be used for systolic volume without further validation.

**Accuracy**

Stroke volume measured from the cineradiographs gave average values similar to those obtained from the flowmeter. However, this type of validation has three drawbacks. (a) The radiographic stroke volume depends on an unreliable measurement of end-systolic volume. (b) This method checks only the change in volume from end-diastole to end-systole, not the actual volumes. (c) Stroke volume by the two methods could only be plotted over a narrow range of values which were far from the origin; the correlation coefficient of 0.70 which was obtained therefore had little meaning.

The possible errors introduced by setting up the geometry of the biplane system, distortion in the image amplifiers, the tracing of the films, the computer program, and changing the shape of the cavity were assessed in total by the following method. Casts of the left ventricular cavity were made of silicone rubber containing contrast medium. The volumes of the casts were determined by the x-ray method and by Archimedes’ principle; they ranged from 20 to 80 ml. The shapes ranged from narrow and irregular, obtained in contracted ventricles, to globular, obtained from dilated ventricles. The relationship of volume (ml) calculated from the x-rays (y) to the true volume (x) was \( y = 1.04x - 7.7, r = 0.986, S_{y|x} = 0.086 \); (standard deviation from regression) = 2.1; the mean volume of the casts was 45 ml. This formula cannot be applied to angiograms because the latter are much more radiopaque and papillary muscles are included in the volume instead of excluded as with the casts; the cast experiment merely checks the geometry and calculations. An additional error was present when using markers...
because the outline of the cavity during the experiments was not continuous. This was assessed by filling a postmortem heart (labeled with tantalum screws) with known amounts of saline (x). The volume calculated from the x-rays (y) was given by \( y = 1.15x + 10.1 \) (Fig. 2), \( r = 0.993 \), \( S_{yx} = 2.31 \); the mean volume of saline injected was 45 ml and the range 20 ml to 70 ml.

Figure 2 shows that the method gives a value for volume that is linearly related to the true volume but is liable to a systematic error because the position of the screws is such that drawing a line between them (Fig. 3) includes some papillary muscle or endocardium (leading to an overestimate of volume) or excludes part of the cavity (leading to an underestimate of volume); the net effect was an overestimate. However, since the slope of the regression line (Fig. 2) is close to 1.0, the error in measurement of changes of volume will be small. Clearly, the magnitude of the error varies with each heart, depending on the position of the screws. We do not believe that the postmortem calibration (Fig. 2) should be applied to the in-vivo measurements because (a) the shape of the ventricle is distorted by the insertion of obturators into the aortic and mitral valves and the use of ligatures to obtain a leakproof seal and by the very great decrease in distensibility compared with the in-vivo situation (this occurs in our hands even with the most rapid preparation of the postmortem heart) and (b) the projection of the left ventricular cavity on to the plane perpendicular to the x-ray beam is slightly different in vivo and after death even when great care is taken in positioning the heart.

The fact that the calculated volume is linearly related to the volume of the postmortem heart does not necessarily mean that the same in true in vivo. Unfortunately, there is at present no way of knowing what the in-vivo volume of the left ventricle really is.

We believe that the good reproducibility of our method and the demonstrated relationship to volume entitles us to use it for studying changes in volume. However, it is not possible to satisfactorily test any method for the measurement of absolute volume because there is no way of knowing how much blood is contained in the normally functioning heart. All measurements of ventricular volume by radio-
graphic and indicator dilution methods are thus liable to unknown systematic errors. An overestimate in the volume measurements will affect the pressure-volume curves, but since the slope of the regression line in Figure 2 is close to 1.0, the principal effect of the error is to shift the curves to the right; there will be little effect on the shape of the curves. A practical disadvantage of our method is the long time required for analysis and consequent limited yield of numerical data.

**CRITIQUE OF LEFT VENTRICULAR PRESSURE MEASUREMENT USING THE 1017 PRESSURE TRANSDUCER**

**Zero Stability.**—With the gauge lying in a water bath at 38.5°C, there was no detectable base-line shift on the high sensitivity diastolic pressure channel over a period of 2 hours. The measurement of changes of pressure over the short periods involved in these experiments (5 min) were therefore almost certainly not affected by base-line drift.

The zero was found to be the same before and after implantation but it is impossible to be certain that there were no shifts in base-line in the intervening period. No change was found from day to day during in-vitro tests. The pressure measurements, like the volume measurements, are therefore subject to an unknown, although very much smaller, systematic error. This error will only affect the value for “a” in the pressure-volume curves, i.e., their position relative to the pressure axis. Changes in position of the pressure-volume curves between control and experimental periods are accurately measured. The error does not affect the shapes of the curves.

**Static Calibration.**—The gauge was linear from 0 to 300 mm Hg and showed no hysteresis. The gain has remained constant over a period of a year.

**Hydrostatic Level.**—The pressure measured by the 1017 gauge will be affected by its vertical position in relation to the rest of the heart and the body. This vertical position may change during the cardiac cycle.

The gauge was implanted in the anterior wall of the heart (Fig. 4), except in one dog in which it was implanted through the apex (Fig. 1). Because the dogs were lying on their right sides, the right lateral border of the heart was in the lowest vertical position and the left lateral border was in the highest vertical position. The 1017 gauge was approximately halfway between these two vertical heights, in the anterior wall.

The changes in vertical height of the transducer were measured from horizontal x-rays. The reference was a fixed point on the x-ray machine (the lower shutter). These measurements were made for successive frames over a cardiac cycle including the end-diastolic and end-systolic points. The maximum difference in vertical height was 0.45 cm. It is therefore unlikely that a sizeable error is introduced by changes in vertical height of the transducer during the cardiac cycle.

Changes in vertical position caused by respiration were eliminated by always making the analyses during the expiratory pause. If there was any change in body position the records were discarded and the experiment repeated. This eliminated change in body position as a source of error.

**Frequency Response.**—We attempted to measure the natural frequency of the gauge using the step-pressure ("pop") technique (12, 13), and a resonant frequency of 3000 cps was recorded. However, this is probably the natural frequency of the test chamber; the natural frequency of the gauge is stated to be 20,000 cps.

**Velocity.**—When blood impinges on the surface of the 1017 gauge there is, in addition to the static pressure, a pressure due to the dissipation of kinetic energy. To avoid this, the transducer was implanted so that it lay next to the wall of the heart. It was sutured to the heart so...
that it moved outward with the wall during diastole. Thus the velocity of the blood relative to that of the gauge and the wall would be small.

The pressure waveform was checked by exposing the right brachial artery under local anesthetic and introducing a Statham SF-1 catheter-tip manometer into the left ventricle. The manometer was fitted with a tip with a closed end and a side hole to minimize velocity effects on this gauge. It was calibrated and checked for zero by means of the pressure recorded through the lumen of the catheter with a Statham P23Dc pressure transducer.

The waveform during diastole from the two gauges was almost identical (Fig. 5) even though one was at the wall (1017) and one out in the cavity (SF-1); they were therefore presumably subjected to different blood velocities. (Some small differences between the two pressures would be expected if there is any flow of blood from one manometer to the other.) This result (Fig. 5) is circumstantial evidence that the velocity effect with the 1017 gauge, used in this particular way, is negligible.

**Results**

In all the dogs studied, left ventricular filling was characterized by an early filling phase lasting 48 to 80 msec; the most rapid movement of the tantalum markers during the cardiac cycle occurred at this time. This was followed by a period of little or no filling lasting 80 to 270 msec (diastasis) and then there was a period of late filling associated with the "a" wave of the left ventricular pressure lasting 48 to 100 msec. These filling events are depicted in Figure 6. The mean increase in volume for the first third of diastole was 0.63 ml/kg, for the second third 0.12 ml/kg, and the last third 0.30 ml/kg. The principal effect of increased heart rate was a reduction in the duration of diastasis (Fig. 7).

The relationship between pressure (P) and volume (V) could be fitted by an exponential curve (Fig. 8) and was expressed by the equation $P = -a + be^{V}$, where $a$, $b$, $e$...
and $c$ are positive constants. The pressure-volume curve was not altered by a change of heart rate in the three dogs in which it was studied (Fig. 9, Table 2). The points obtained after saline infusion (in the 4 dogs studied) were not significantly different from the control over the range where the data points overlapped. The control and saline points have been pooled to obtain the equations for the pressure-volume curves in Table 1.

Injections of calcium gluconate (two dogs) had no effect on the pressure-volume relationship (Fig. 10). Following injections of isoproterenol (2 dogs), there was no change in the relationship between pressure and volume during diastasis but during early and late diastolic filling, the points were to the left of the control curve in both dogs (Fig. 11). Methoxamine also produced a shift to the left of the points during early and late diastolic filling (Fig. 12), but again there was no change in the relationship between pressure and volume during diastasis.

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1As we stated in the methods, there is no satisfactory way of comparing these exponential data statistically. When the whole of the saline data was compared with the control, it was not possible to use logarithmic plots because of the great discrepancy between the variances. The variance of the saline points from the exponential curve fitted to them was compared with the variance of the same points from the extrapolation of the exponential curve fitted to the control data alone. An analysis of covariance was also done between the saline points and control points when $P$ was plotted against $V$ (this gives a linear relationship). Both these methods of analysis showed that the saline points were significantly above the extrapolated control line; the validity of such extrapolation, however, is in doubt. No method of statistical analysis ever showed that the saline points were below the control line.

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Table 2

Effect of Heart Rate on the Diastolic Pressure-Volume Relationship

<table>
<thead>
<tr>
<th>Dog</th>
<th>Heart rate (beats/min)</th>
<th>Equation for exponential fit</th>
<th>S</th>
<th>r</th>
</tr>
</thead>
<tbody>
<tr>
<td>J</td>
<td>108</td>
<td>( P = -0.28 + 0.08e^{0.96V} )</td>
<td>0.63</td>
<td>0.97</td>
</tr>
<tr>
<td></td>
<td>108 and 141*</td>
<td>( P = -5.80 + 2.13e^{0.63V} )</td>
<td>1.16</td>
<td>0.90</td>
</tr>
<tr>
<td>L</td>
<td>97</td>
<td>( P = -3.21 + 0.19e^{0.97V} )</td>
<td>1.04</td>
<td>0.89</td>
</tr>
<tr>
<td></td>
<td>154</td>
<td>( P = -1.23 + 0.16e^{0.87V} )</td>
<td>1.38</td>
<td>0.75</td>
</tr>
<tr>
<td></td>
<td>97 and 154*</td>
<td>( P = -1.34 + 0.15e^{0.70V} )</td>
<td>1.17</td>
<td>0.90</td>
</tr>
<tr>
<td>Q</td>
<td>123</td>
<td>( P = -6.03 + 0.40e^{0.25V} )</td>
<td>6.15</td>
<td>0.90</td>
</tr>
<tr>
<td></td>
<td>123 and 160*</td>
<td>( P = -2.89 + 0.23e^{0.14V} )</td>
<td>7.01</td>
<td>0.85</td>
</tr>
</tbody>
</table>

Notation as in Table 1.

*Equation obtained by pooling data from the two heart rates. It was not possible to fit an exponential expression to the data on high heart rates in dogs J and Q because the data were scattered and covered only a narrow range of volumes (low stroke volume). In dogs L and Q, the high heart rate data was within 2 SD of the estimate for the low heart rate. In dog J, some data points at 141 beats/min were outside 2 SD of the estimate for 108/min, but these points were scattered on either side of the line. No significance was therefore attached to the differences in the pressure-volume data for the two heart rates in each dog.

![Figure 10](image1.png)

**FIGURE 10**

Relationship between left ventricular pressure and volume during diastole in dog T. The continuous line was obtained by exponential fit to data under control and saline-loaded conditions, \( P = -1.05 + 0.02e^{0.61V} \). Saline produced a 4.7% increase in LV dp/dt max and no change in the maximum acceleration of blood from the left ventricle. The mean filling rate for the first 1/30 second of diastole increased from 0.41 to 0.50 ml/msec. Pressure-volume data were then obtained after injection of 32 mg/kg calcium gluconate (solid circles), which produced a 27.3% increase in LV dp/dt max over the saline value and a 38.1% increase of maximum acceleration. The mean filling rate for the first 1/30 second of diastole was 0.30 ml/msec. All the calcium data points were within 2 SD of the control line.

![Figure 11](image2.png)

**FIGURE 11**

Relationship between left ventricular pressure and volume (dog Q) under control conditions and 30 seconds later, after injection of 1 µg isoproterenol. The heart rate increased from 100/min to 150/min and LV dp/dt max rose 17.5%. (Larger doses produced excitement and movement of the dog). Mean filling rate for the first 1/30 second of diastole increased from 0.03 to 0.10 ml/msec. Dashed line drawn by eye through the isoproterenol data. Circled point was the only one outside 2 SD from the control line.

**Discussion**

**LEFT VENTRICULAR FILLING**

We have demonstrated that in the resting conscious dog, left ventricular filling occurs almost entirely during early and late diastole (Fig. 6). Rushmer and his co-workers...
Relationship between left ventricular pressure and volume during diastole in dog T. The continuous line was obtained by exponential fit to the data under control and saline-loaded conditions, \( P = -1.06 + 0.02e^{-0.02} \). Pressure-volume data were then obtained after injection of 0.08 mg/kg methoxamine (solid circles), which produced an increase of systolic left ventricular pressure from 141 mm Hg to 158 mm Hg; heart rate slowed from 114 beats/min to 60 beats/min. (Systolic hypertension was limited by gross bradycardia.) Maximum acceleration of blood from left ventricle fell by 5.3%. LV dp/dt max rose by 5.3% and mean filling rate for the first 1/30 second of diastole increased from 0.41 to 0.95 ml/msec. Dashed line drawn by eye through the methoxamine data. Circled points are outside 2 SD from the control line.

found that virtually all filling took place in early diastole (14, 15); Rushmer used anesthetized dogs, and this may account for the difference in results. In addition, his use of injected contrast medium may have altered the filling dynamics. Chapman et al. (9) also found little filling in late diastole using injected Hypaque in anesthetized dogs, but unlike Rushmer (14, 15) observed no period of diastasis.

Changes in dimensions of the left ventricle have been measured in unanesthetized dogs using chronically implanted gauges, but the results are conflicting. Bushmer and his co-workers (16, 17) measured the internal dimensions of the cavity with variable inductance gauges and the circumference with a mercury and rubber strain gauge. Their tracings show a considerable amount of late diastolic filling. Hawthorne (18) measured the external cross-sectional area of the left ventricle with an electromagnetic method and external circumference with a mercury and rubber strain gauge. After the sixth postoperative day (but not before) he found changes in these dimensions in diastole that were similar to our results for volume. Ninomiya and Wilson (19), using mutual inductance gauges to measure external diameter, showed little late diastolic filling in their published tracing. These methods have the advantage of giving a continuous record of changes in dimension but have the disadvantage that these changes can be caused by an isovolumic alteration of the shape of the ventricle.

Our results suggest that an appreciable amount of filling takes place at the time of atrial systole, presumably as a result of atrial contraction. Linden and Mitchell (20) studied variable timing of atrial systole and came to a similar conclusion. At higher heart rates the left ventricle filled less and diastasis was curtailed (Fig. 7). We conclude that early and late diastole are the main times when left ventricular filling occurs. A period of relatively little filling (diastasis) occurs in mid-diastole, the duration of which varies with heart rate.

**DIASTOLIC PRESSURE-VOLUME RELATIONSHIP**

The relationship between diastolic pressure and volume has not previously been determined in the conscious dog. It was found to be approximately exponential. The close correlation between these two variables (Table 1) suggests that the relationship is mainly determined by the elastic properties of the ventricle. The curvilinear nature of the relationship could be explained by viscous properties that result in higher pressures during times of rapid filling (early and late diastole) than would be obtained from the purely elastic pressure-volume relationship. However, since the late filling points are not higher than the diastasis points following saline infusion (Fig. 8), this explanation is unlikely. However inertial, viscous and plastic properties would be expected to produce a considerable amount
of scatter in the data (21, 22). (In this discussion we have assumed that residual activity of the contractile mechanism in diastole will manifest itself as elastic properties (force depending on length) or viscous properties (force depending on velocity of lengthening) which behave as if in parallel with a freely extensible contractile element).

We conclude that the elastic pressure-volume relationship is curvilinear as is the diastolic force-length relationship (23).

**Viscous Properties of the Left Ventricle in Diastole**

The viscous properties of the ventricle would produce an excess of pressure (relative to the elastic pressure-volume curve) at times of rapid increase in volume. This effect may contribute to the scatter (Fig. 8), but does not appear to produce much deviation from the presumed compliance curve under control conditions or at high heart rate (Fig. 9).

The effect may be brought out by the administration of isoproterenol, which both shortens the duration of diastole and increases the rate of filling. This drug did produce a shift to the left of the points measured during the rapid early and late diastolic filling (Fig. 11). Methoxamine also increased the speed of filling, presumably because of the high left atrial pressure; this drug altered the pressure-volume curve in a manner similar to that of isoproterenol (Fig. 12).

The presence of viscous effects renders unreliable the use of end-diastolic pressure as an index of end-diastolic volume or initial fiber length because this pressure partly depends on a variable rate of change of volume at the end of diastole.

**Evidence for a Series Viscous Element**

The viscous properties in diastole could behave as if they were in parallel or in series with the contractile element during systole. Sonnenblick et al. (24) suggested that heart muscle behaved as if there was a viscous element in series with the contractile element and the parallel elastic element. They showed that the diastolic force for a given length in papillary muscle (or the diastolic pressure for a given volume in the isovolumic ventricle) decreased when the force (pressure) during the previous systole was increased. This can be explained by saying that the increased force of the contractile element produced a greater velocity of lengthening of the series viscous element. Consequently, the series viscous element was longer in the following diastole. If the series viscous element was in series with the parallel elastic element, the latter was shorter and sustained less force. If this phenomenon is present in the conscious dog, there should be a shift to the right of the pressure-volume curve following a rise in systolic pressure. This did not occur (Fig. 12). Braunwald et al. (25) also found no such change in the pressure-circumference curve of the open-chest dog.

We conclude that the series viscous element is not an important determinant of the diastolic pressure-volume relationship in these preparations. Since there is little evidence for a series viscous element, the viscous properties are probably in parallel with the contractile element and could be related to viscous resistance to extension of the sarcomeres or of supporting tissue.

**Inertial Properties of the Left Ventricle in Diastole**

The inertial properties would increase the pressure (relative to the elastic pressure-volume curve) when the left ventricular wall was accelerating outward and decrease the pressure when the wall of the ventricle was decelerating. These effects are probably very small since the velocities of radial wall movement are low. However, the end-diastolic pressure sometimes occurred following a presystolic “dip” in the pressure wave (Fig. 6), which was not usually accompanied by so much movement of the tantalum markers. This gave rise to a pressure-volume point below the calculated curve (e.g., end-diastolic pressure following saline, solid diamond in Fig. 8). A possible reason for this is the abrupt end to late diastolic filling at this time (i.e., deceleration).
This is an additional factor tending to make end-diastolic pressure an unreliable index of end-diastolic volume or, if end-diastolic volume is known, of compliance.

PLASTIC PROPERTIES OF THE LEFT VENTRICLE IN DIASTOLE

We have called slow, time-dependent changes in the physical properties of the ventricle (e.g., "stress relaxation," "creep," etc., "plastic properties" (22) even though they may be reversible. Plastic properties would manifest themselves when the ventricle was subjected to a prolonged stretch (22) by infusion of saline to increase left ventricular volume (Fig. 8) over a period of 10 minutes or more. This would cause the muscle to "give" so that the pressure would fall for a given volume or the ventricle would dilate at a constant pressure (22). In our experiment, the points measured after the infusion would lie to the right of the control points. There was never any shift of this kind over the range where control and saline data overlapped (Fig. 8). Any slight changes that did occur were in the opposite direction. Plastic properties would also be expected to shift the methoxamine pressure-volume curve to the right (because the ventricle was unable to empty adequately against the high pressure and became distended); no such shift occurred.

The plastic properties of the left ventricle thus appear to be too small to be detected by our methods and are probably unimportant in this preparation.

DIASTOLIC SUCTION

Another possible influence on the pressure-volume curve is that the ventricle may contract to end-systolic volumes below the volume of elastic equilibrium (26) so that the beginning of diastole occurred with release of potential elastic energy and a "suction" effect (27, 28).

We do not believe that this factor was important in our experiments for the following reasons: (a) All our end-systolic volumes were above the volume of elastic equilibrium calculated from the data of Brecher et al. (26) for excised hearts. (b) When isoproterenol, which produces vasodilatation, and a fall of end-systolic volume was used, saline was infused to keep the end-systolic volume above the equilibrium volume. (c) If the suction effect occurred, one would expect early diastolic pressures below the line obtained by extrapolating the mid-to-late diastolic pressure-volume relationship, but this was not so. Indeed, isoproterenol produced pressures above the control pressure-volume curve in early diastole. (d) There was a symmetrical outward movement of the tantalum markers throughout diastole, whereas one would expect that restoration of a larger equilibrium volume would be associated with a change in shape (as with a squashed tennis ball).

It is likely that the high aortic pressure in our experiments compared with the excised hearts of Brecher et al. (26) prevented the heart from contracting down below the volume of elastic equilibrium (29). Diastolic suction is unlikely to be an important determinant of ventricular filling in normal circumstances but may come into play when peripheral resistance is low.

EFFECT OF A CHANGE OF CONTRACTILITY ON THE ELASTIC PROPERTIES OF THE LEFT VENTRICLE IN DIASTOLE

The infusions of calcium gluconate produced an increase of myocardial contractility without changing the speed of filling; there was no detectable deviation of the pressure-volume curve (Fig. 10) suggesting that the elastic properties of the ventricle were unaltered. There was also no change in the position of the diastasis points when contractility was increased with isoproterenol.

Rushmer (30) described fluctuations in the diastolic pressure-circumference relationship during epinephrine infusion. However, it seems possible that the apparent changes in maximum circumference seen in his published tracing are in fact due to an increase in the maximum circumference during isovolumic systole. Hefner et al. (21) found a shift to the right of the pressure-circumference relationship in anesthetized open-chest dogs following epinephrine infusion. These authors were careful to consider all the fac-
tors discussed here but the "plastic" behavior in their preparation was not determined. It is possible that, since they obtained their data by producing slow changes in ventricular volume, the results may have been affected by "plastic deformation" (22). Other experiments have not shown any change in distensibility (31, 32) with interventions that change myocardial contractility. The purely elastic properties of the normal ventricle in diastole are probably unaffected by an increase in the contractile strength of the muscle. The effect of pathologic changes remains to be explored.

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