Diasstolic Pressure-Volume Relationship in the Canine Left Ventricle

By George Diamond, James S. Forrester, James Hargis, William W. Parmley, Ronald Danzig, and H. J. C. Swan

ABSTRACT

Analysis of the passive pressure-volume filling curve of the left ventricle demonstrates that heart size and ventricular geometry exert major effects on the pressure-volume curve in the absence of changes in intrinsic muscle stiffness. Because the pressure-volume relationship is curvilinear, both quantitative and qualitative comparison of pressure-volume curves from different hearts is difficult. In the fresh isolated canine left ventricle, the pressure-volume relation was found to be almost perfectly exponential throughout a range of filling pressures from 5 to 30 mm Hg. Therefore, a precise linear and quantitative expression of the pressure-volume relation (dP/dV = aP + b) was developed (r = 0.995). The effect of isolated changes in either initial ventricular volume (mean Δa = 3.1%) or ventricular geometry (mean Δa = 27.1%) upon the slope, or a constant of this function was small in comparison to changes induced by rigor mortis (mean Δa = 45%). It was concluded that the a constant was primarily affected by changes in left ventricular wall stiffness. In this manner, comparison of the pressure-volume relationship from different hearts is possible, and the contribution of changes in wall stiffness may be quantified.

KEY WORDS compliance ventricular geometry ventricular volume ventricular wall stiffness ventricular end-diastolic pressure rigor mortis passive elastic modulus

The ratio of end-diastolic volume to pressure (EDV/EDP), or the change in ventricular volume per unit change in ventricular pressure (ΔV/ΔP) has been used as a quantitative estimate of left ventricular compliance in both isolated and intact hearts (1-7). Other investigators have employed the reciprocal (ΔP/ΔV) for evaluation of changes in ventricular stiffness (4, 6, 8). Such values are assumed to reflect changes in the elastic properties of ventricular muscle. However, certain important assumptions are violated in the use of such indices as a measure of the intrinsic stiffness of the myocardium.

The first relates to the curvilinear nature of the ventricular P-V relationship. "Observed compliance," as determined by the ratio ΔV/ΔP, varies with the portion of the curve analyzed (9). In the range of normal ventricular filling pressure, the P-V curve is relatively flat, and therefore observed compliance is great. However, as ventricular filling pressure increases, the P-V curve becomes steeper, and observed compliance consequently decreases in the absence of any intrinsic change in muscle stiffness. It is thus impossible to compare P-V curves on the basis of the ratio ΔV/ΔP without specifying a discrete value for P. Any simple ratio of pressure to volume becomes inadequate, therefore, as an index of ventricular stiffness (10).

Second, the stiffness of isolated muscle is only one of several determinants of the P-V relationship and overall ventricular compliance. Other factors—specifically, chamber size, geometry, and wall thickness—contribute to the final P-V relationship. Although these factors may remain relatively constant within...
a given heart over long periods of time, they vary enough from heart to heart to render ratios of pressure to volume of limited value as a comparative index of muscle stiffness.

The purpose of this study was to develop an appropriate mathematical description of the P-V relationship, define its determinants in the isolated anoxic-arrested canine left ventricle, and develop a quantitative index of ventricular wall stiffness which is largely independent of chamber size and geometry.

Methods

Eight mongrel dogs weighing 15--22 kg were used. After anesthesia with pentobarbital sodium 30 mg/kg iv, the chest was rapidly opened and the heart was dissected free of the pericardium and intrathoracic organs. The left ventricle was washed free of blood with Ringer-lactate. A 40-cm nondistensible 10F tube was passed across the aortic valve via the aortic root. A second was passed across the mitral valve via a pulmonary vein and both were advanced into the midpoint of the left ventricular cavity. These catheters were secured by a heavy cotton tie about the atrioventricular groove. The "aortic" catheter was attached directly to a Statham P23dB pressure transducer. The "mitral" catheter was attached to a double track Harvard constant infusion pump equipped with 50-ml plastic syringes and calibrated to deliver 5.50 ml/sec. The pump rate was accurate to 1%. The heart was suspended from a ringstand via a hemostat affixed to the transsected aortic root and was immersed in a bath of Ringer-lactate at 23°C to the superior surface of the left ventricle so as to equalize stresses across its wall. The transducer was then positioned at the surface of the immersion bath. The average time required for this procedure was approximately 5, and in no case was greater than 10, minutes.

Simultaneous right and left ventricular filling is known to alter the P-V relationship (7). Since only comparative changes in left ventricular compliance were considered, these effects of right ventricular filling were excluded in this study. The left ventricle was filled with Ringer-lactate to a pressure of 30 mm Hg while the right ventricle remained empty. The absence of escaping entrapped air bubbles into the bath served to document the adequacy of a sealed system. Entrapped air was subsequently removed via the mitral catheter by repeated gentle manual compression of the left ventricle sufficient to completely obliterate the chamber. A stopcock at the transducer was then opened and the left ventricle allowed to drain to atmospheric pressure. The chamber volume at this pressure (V0) (volume at P = 0 mm Hg) was then determined to the nearest 0.5 ml by siphon drainage into a graduated cylinder. Since a pressure gradient existed between the heart in its immersion bath and the graduated cylinder below this level, complete obliteration of the left ventricular chamber occurred during this maneuver. The variability of multiple determinations of V0 by this technique was less than 0.5 ml. The ventricle was then refilled to V0. The ventricle was filled from the Harvard pump to a volume at which P = 30 mm Hg, at which time the pump was switched to reverse mode and fluid was withdrawn at constant rate to P = 0. The pressure-time relationships (filling and emptying) were recorded in duplicate on either Honeywell or Electronics for Medicine photographic recorders at a paper speed of 25 or 50 mm/sec with 0.1-second time lines. The time required for each determination was less than 30 seconds. Since infusion rate is constant, volume can be substituted for the time axis. To evaluate the influence of ventricular chamber size and shape on the P-V relationship, initial ventricular volume and chamber geometry were varied by the application of a large Satinsky clamp in such a way as to exclude either the apex or the free lateral wall of the left ventricle. Placement of the clamp along the long axis of the chamber (longitudinal clamping) maintained the general ovoid shape of the chamber, but decreased chamber size and, thus, V0. By exclusion of the apex (cross clamping), V0 was similarly decreased. Moreover, the general geometry of the ventricle was modified to more closely approximate a sphere. The nature of these geometric alterations was established in six dogs by left ventricular casts produced by injection of polyvinyl chloride. Residual new V0's and P-V curves were obtained during and immediately following both clamping procedures on seven of the eight hearts. Four hearts were restudied 3 hours after death to determine the changes occurring with the development of rigor mortis. At the completion of study, the right ventricle, atria and great vessels were dissected away from the left ventricle and the empty chamber was weighed to the nearest gram. Mean ventricular wall thickness (h) was calculated, assuming a spherical geometry and a specific gravity of muscle of 1.0, as follows:

\[ h = 0.62 \left( \frac{\pi}{6} V_{wt} + V_n - V_0 \right) \]

Pressures and volumes were measured directly from the recorded curves, and instantaneous \( dP/dV \) was approximated by determining \( \Delta P/\Delta V \) at 0.1-second intervals for the entire range of the curve corresponding to increments of added volume of 0.550 ml. The cumulative error
of this determination is less than 1%. The mathematical constants relating dP/dV to intraventricular pressure were calculated by digital and analogue computer techniques.

Results

Theoretical Considerations

To facilitate experimental design and data analysis, certain assumptions regarding the ventricular pressure-volume relationship were made. The isolated length-tension relationship of cat papillary muscle is perfectly exponential (unpublished observations). Since length-tension characteristics of isolated muscle must be a major determinant of the P-V relationship, it was assumed that the ventricular P-V relationship is also exponential. On this basis, a derived coefficient of ventricular wall stiffness can be obtained which is independent of both pressure and volume. The mathematical argument follows.

The general equation for such an exponential relationship is

\[ P = xe^{aV} - b/a, \]  

where \( P \) and \( V \) are intraventricular pressure and volume; and \( x \), \( a \), and \( b \) are constants.

By differentiation:

\[ \frac{dP}{dV} = axe^{aV}. \]  

Adding \( b/a \) to Eq. 1 and multiplying by \( a \), one obtains

\[ a(P + \frac{b}{a}) = axe^{aV}. \]  

By subtracting Eq. 2 from Eq. 3,

\[ \frac{dP}{dV} = aP + b. \]  

By differentiation of Eq. 4 with respect to pressure,

\[ \frac{d}{dP} \frac{dP}{dV} = a. \]  

Thus, the constant \( a \) is mathematically independent of both pressure and volume and is a measure of the rate of change of instantaneous
stiffness (dP/dV). The unit of measurement of a is ml⁻¹, and of b, mm Hg/ml. The constants a and b may be derived graphically from Eq. 4. The relation of dP/dV to P is linear with a slope a and intercept with the ordinate b.

**RELATIONSHIP BETWEEN INSTANTANEOUS dP/dV AND INTRAVENTRICULAR PRESSURE**

Figure 1 is that of a typical P-V curve obtained from an anoxic-arrested canine left ventricle. A plot of derived dP/dV against intraventricular pressure for this same heart is seen in Figure 2. There is a precise linear relationship between these two variables throughout the range of intraventricular pressure from 7 to 24 mm Hg. The mean coefficient of correlation for 112 separate P-V curves in eight hearts was 0.995 (range, 0.986-0.998). The variability of duplicate determinations was 3.5%. It was further noted that there are two distinct mathematically describable regions to the P-V curve (Fig. 3). Below a certain pressure, Pm, in the normal ventricle, dP/dV is constant. This relationship may be expressed as

\[
\frac{dP}{dV} = m. \tag{6}
\]

By integration, and evaluation of the constant of integration at P = 0,

\[
V - V_0 = \frac{P}{m}, \text{ where } 0 \leq P \leq Pm. \tag{7}
\]

The value of Pm was 2.5 ± 0.7 mm Hg in the eight hearts. At pressures greater than Pm,

\[
\frac{dP}{dV} = aP + b. \tag{4}
\]

Integration of Eq. 4 yields

\[
V = \frac{\ln(aP + b)}{a} + C, \tag{8}
\]

where P ≥ Pm and C is a constant of integration. The constant of integration must be evaluated at any pressure, P ≥ Pm, and a known volume at that pressure (Table 1). Figure 4 demonstrates the accuracy of a predicted P-V curve obtained following evaluation of the constants a, b, m and C in

**FIGURE 3**

Schematic representation of the bimodal linear relationship of dP/dV and P illustrated in Figure 2.

**FIGURE 4**

Comparison of the actual P-V curve illustrated in Figure 1 and that predicted from derived constants by analysis of the relationship of dP/dV and P. Note the precise correlation between the predicted and experimental values.
Derived Constants for P-V Curves

<table>
<thead>
<tr>
<th>Dog</th>
<th>a (ml⁻¹)</th>
<th>b (mm Hg/ml)</th>
<th>C (ml)</th>
<th>V₀ (ml)</th>
<th>m (mm Hg/ml)</th>
<th>Pm (mm Hg)</th>
<th>h (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.112</td>
<td>-0.072</td>
<td>49.8</td>
<td>31.0</td>
<td>0.047</td>
<td>1.1</td>
<td>1.54</td>
</tr>
<tr>
<td>2</td>
<td>0.072</td>
<td>-0.028</td>
<td>71.5</td>
<td>30.0</td>
<td>0.012</td>
<td>0.5</td>
<td>1.26</td>
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<tr>
<td>3</td>
<td>0.117</td>
<td>-0.093</td>
<td>49.2</td>
<td>25.0</td>
<td>0.051</td>
<td>1.3</td>
<td>1.44</td>
</tr>
<tr>
<td>4</td>
<td>0.090</td>
<td>-0.175</td>
<td>84.4</td>
<td>41.0</td>
<td>0.073</td>
<td>2.7</td>
<td>1.38</td>
</tr>
<tr>
<td>5</td>
<td>0.074</td>
<td>-0.060</td>
<td>83.0</td>
<td>43.0</td>
<td>0.056</td>
<td>1.5</td>
<td>1.38</td>
</tr>
<tr>
<td>6</td>
<td>0.097</td>
<td>-0.615</td>
<td>81.5</td>
<td>23.0</td>
<td>0.156</td>
<td>6.6</td>
<td>1.18</td>
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<tr>
<td>7</td>
<td>0.119</td>
<td>-0.453</td>
<td>70.4</td>
<td>26.0</td>
<td>0.096</td>
<td>4.6</td>
<td>0.96</td>
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<tr>
<td>8</td>
<td>0.068</td>
<td>-0.110</td>
<td>52.1</td>
<td>23.5</td>
<td>0.048</td>
<td>1.9</td>
<td>0.93</td>
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**Control**

<table>
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<tr>
<th>Post-Clamp</th>
<th>0.084</th>
<th>-0.106</th>
<th>67.2</th>
<th>0.042</th>
<th>1.8</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.099</td>
<td>-0.237</td>
<td>51.6</td>
<td>0.114</td>
<td>1.8</td>
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<tr>
<td></td>
<td>0.077</td>
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<td>0.030</td>
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<td>0.030</td>
<td>2.0</td>
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<tr>
<td></td>
<td>0.090</td>
<td>-0.185</td>
<td>54.9</td>
<td>0.075</td>
<td>2.7</td>
</tr>
<tr>
<td></td>
<td>0.121</td>
<td>-0.504</td>
<td>67.8</td>
<td>0.112</td>
<td>5.1</td>
</tr>
<tr>
<td></td>
<td>0.098</td>
<td>-0.110</td>
<td>52.1</td>
<td>0.048</td>
<td>1.9</td>
</tr>
</tbody>
</table>

**Longitudinally Clamped**

| Cross-Clamped | 0.088 | 0.420 | 17.1 | 8.0 | 0.42 | 0.0 |
|              | 0.124 | 1.350 | 10.6 | 13.0 | 0.05 | 0.0 |
|              | 0.061 | 2.200 | 47.6 | 22.0 | 0.00 | 0.0 |
|              | 0.057 | 0.379 | 45.3 | 23.0 | 0.00 | 0.0 |
|              | 0.084 | 0.014 | 29.0 | 13.0 | 0.00 | 0.0 |
|              | 0.121 | 0.466 | 41.8 | 14.0 | 0.00 | 0.0 |
|              | 0.113 | 0.117 | 27.2 | 12.5 | 0.00 | 0.0 |

**Rigor Mortis**

|          | 0.106 | 0.145 | 26.4 | 17.0 | 0.0  | 0.0 |
|          | 0.094 | 0.256 | 32.0 | 17.0 | 0.0  | 0.0 |
|          | 0.042 | 0.396 | 49.3 | 22.0 | 0.0  | 0.0 |
|          | 0.038 | 0.381 | 46.7 | 23.0 | 0.0  | 0.0 |
|          | 0.060 | 0.538 | 23.8 | 14.0 | 0.0  | 0.0 |
|          | 0.093 | -0.092 | 41.8 | 17.5 | 0.055 | 1.6 |
|          | 0.084 | 0.182 | 31.1 | 16.0 | 0.0  | 0.0 |

For abbreviations, see text.

Comparison to the actual experimental curve. The average variance in 112 P-V curves was 2.5%. MAJOR DETERMINANTS OF THE PRESSURE-VOLUME RELATIONSHIP (TABLE 1, FIG. 5).

**Initial Ventricular Volume (V₀).**—To define the relationship of chamber size to the a and b constants, initial ventricular volume (V₀) was varied by longitudinal clamping of the left ventricle. The effect of this procedure was to markedly shift the P-V curve to the left (Fig. 5, top). Normalization of the P-V data for respective initial ventricular volumes, however, resulted in only a small but statistically significant difference (P < 0.05) between the two P-V curves (Fig. 5, bottom).

Figure 6 demonstrates that there was always an increase in the b constant, although of variable magnitude, concomitant with a decrease in V₀. Whenever b has a value greater than zero, the initial linear portion of the P-V curve is eliminated and the curve becomes entirely exponential. There was no change in the a constant following longitudi-
Top: Mean pressure-volume curves obtained from eight isolated canine hearts, before and following various interventions. The P-V curves obtained after removal of the clamp are unchanged from control. Note especially the shift to the left of control associated with a decrease in chamber size. Bottom: Same curves normalized for initial chamber size. Note that the curve for cross-clamping now falls to the right of control while that for longitudinal clamping is slightly to the left of control. The curve for rigor mortis remains markedly shifted to the left.

Discussion

Whereas it is well known that the pressure-volume relationship is not linear (11, 12) and that compliance is inversely related to intraventricular pressure (9), there have been no direct attempts at a more complete mathematical analysis. Thus, compliance, although conceptually well understood, remains ambiguously defined (10). Lacking definition of the factors significantly influencing the overall relationship of ventricular diastolic pressure to volume, the initial purpose of this study, then, was to determine the effects of major changes similar, the P-V curves obtained on the cross-clamped chambers differed significantly from those obtained on the longitudinally clamped chambers. In comparison to the longitudinally clamped hearts, P-V curves of cross-clamped hearts always lay to the right (Fig. 5). The a and b constants reflected this shift (Table 1). Thus, the a constant was decreased by this geometric alteration. The b constant, which was previously shown to change with initial volume, varied widely and unpredictably following marked geometric alteration. In one heart there was no change, in two a decrease, and in three an increase in b following cross-clamping.

Wall stiffness.—Figure 5 (top) demonstrates the effect of rigor mortis on the isolated P-V curves of four hearts. Chamber size decreased substantially with the development of rigor. The change in chamber size alone, however, does not fully account for the shift of the P-V curve, since normalization of the P-V data for initial volume resulted in comparable curves (Fig. 5, bottom). A plot of mean values of a ± se immediately after death and 3 hours later is seen in Figure 7. There was a 50% increase in a. The b constant was also significantly altered by changes in wall stiffness. Since this constant is sensitive to volume changes as well, however, it is less useful as an index of wall stiffness.

Wall Thickness.—No relationship was found between calculated left ventricular wall thickness (h) and any of the derived constants describing the P-V relationship (a,b,C,m,Pm).
The alterations in $b$ constant associated with a decrease in $V_o$ by longitudinal and cross-clamping. There is a general inverse relationship between $\Delta b$ and $\%AV_o$ with wide variability.

in geometry and initial volume ($V_o$) on the ventricular pressure-volume relationship.

A decrease in intrinsic chamber size, in the absence of altered chamber geometry or wall stiffness, produced a marked shift of the pressure-volume curve to the left of control. This relationship between intrinsic chamber size ($V_o$) and the resultant P-V curve is, in some measure, predictable. The fact that ventricular diastolic pressure is similar in species of disparate size has been explained by the constancy of the ratio of ventricular radius to wall thickness ($r/h$). Thus, according to the Laplace equation, wall stress (and sarcomere length) would be a function only of pressure if geometry were maintained (13). In the present study, longitudinal clamping had the effect of decreasing radius, but did not alter wall thickness. The resultant decrease in the ratio $r/h$ produced a lower wall stress at any corresponding pressure in comparison to control. The P-V curves following longitudinal clamping, therefore, were shifted an average of 20% to the left of control when normalized for differences in $V_o$. This agrees with the shift expected from Laplace considerations. A mean decrease of 50% in $V_o$ (Table 1) would be predicted to result in a 21% decrease in wall stress at a common pressure.

Although pressure-volume curves following geometric alteration were also shifted to the left of control, they fell to the right of curves obtained from ventricles of similar volumes but with unaltered geometry. In these experiments it is not possible to change ventricular volume without concomitant alteration of ventricular geometry. Analysis of the effects of such interventions, therefore, must be made in this context. However, following normalization of resultant pressure-volume curves for initial ventricular volume, spheroid geometry was associated with a pronounced shift of the curves to the right of control. Rigor mortis was associated with an extreme leftward shift, indicating a marked increase in stiffness.

It is apparent from the foregoing that analysis of changes in wall stiffness is not possible from observation of pressure-volume curves alone. Although pressure-volume
curves from hearts of unequal initial (V₀) volumes may differ, wall stiffness (dP/dV) may be identical.

Analysis of passive length-tension curves obtained from isolated cat papillary muscle has demonstrated that a precise exponential relationship exists between these two variables, given by the equation dT/dL = aT + b. The passive pressure-volume relationship of the intact canine heart was found to conform precisely to the analogous relationship dP/dV = aP + b. At pressures of less than 2-5 mm Hg, however, the pressure-volume relationship was linear (with a approaching zero). The factors contributing to this portion of the curve are not defined by our study.

From the above considerations, simple mathematical expressions of the two portions of the pressure-volume curve were developed. In the major exponential portion of the curve, the derived constants a and b were evaluated before and following various interventions. The a constant was unaffected by changes in initial volume and directly altered only by changes in wall stiffness and, to a lesser extent and in an opposite direction, by a more spheroid geometry. The a constant may therefore be used as a quantitative index of wall stiffness in those situations where geometric alterations are slight. In these studies, a 50% increase of a occurred with rigor mortis. The b constant, although also directly related to wall stiffness, was inversely related to the initial volume of the ventricular chamber. Since initial volume may be a significant variable in comparisons from one heart to another, the b constant, therefore, is not applicable to analysis of wall stiffness.

There are, therefore, several factors which determine the shape of the pressure-volume relationship, only one of which is ventricular wall stiffness. Independent variation of any of these determinants results in predictable changes in the pressure-volume curve. Since more than one determinant may vary simultaneously, it is not possible to infer changes in wall stiffness solely from inspection of the pressure-volume curve. By determining the mathematical constants which express the pressure-volume relationship, however, it was possible to isolate a single index, the constant a, which relates directly to wall stiffness, and may be termed the passive elastic modulus. Within the limitations discussed, the a constant may be used to evaluate changes in ventricular wall stiffness in a variety of states.

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