Dynamic Determinants of Left Ventricular Diastolic Pressure-Volume Relations in Man

By William H. Gaasch, M.D., James S. Cole, M.D., Miguel A. Quinones, M.D., and James K. Alexander, M.D.

SUMMARY

Left ventricular (LV) diastolic pressure (P), volume (V), and rate of change of volume (dV/dt) were determined at 16.7 msec intervals in 17 patients (simultaneous micromanometer and single plane volume angiography). Four patients had mitral stenosis with atrial fibrillation and 13 patients (three normal, two congestive cardiomyopathy, three LV hypertrophy, and five coronary artery disease) were in normal sinus rhythm. Maximum early diastolic filling rates (max dV/dt) in the normal and cardiomyopathy patients were similar and ranged from 269 to 370 cc/m2/sec; in coronary artery disease and LV hypertrophy, max dV/dt ranged from 197 to 290 cc/m2/sec and 213 to 255 cc/m2/sec respectively; in mitral stenosis, max dV/dt ranged from 215 to 270 cc/m2/sec. The peak filling rate during atrial systole ranged from 60 to 240 cc/m2/sec in the 13 patients with sinus rhythm.

The instantaneous diastolic P-V data were fit by an exponential equation (P = be^kV) and the P-V relation throughout diastole was represented by the best fit line. The rate constant (k) in the equation was highest in the patient with IHSS and lowest in those with large dilated hearts. In mitral stenosis with atrial fibrillation the fit of the equation to the P-V data appeared better than in the patients with normal sinus rhythm. Peak ventricular filling rate during atrial systole varied directly with LV volume distensibility at the onset of atrial systole (r = 0.64). Data suggest that dynamic mechanical properties of the LV influence the diastolic P-V relations and that pressure ‘deviations’ (ΔP) from the best fit line during atrial systole may be related to viscous drag. In a given ventricle the velocity dependence of ΔP appears to be modified by the volume distensibility of the ventricle. Variable rates of filling may preclude the assumption of an exponential relation between P and V throughout diastole and therefore may limit estimates of diastolic distensibility or compliance which rely on such an assumption.

Additional Indexing Words:

Elastic stiffness
Left ventricular volume

Left ventricular dV/dt

Left ventricular distensibility

Left ventricular compliance

Viscous stiffness

Several varieties of heart disease may produce symptoms caused more by abnormal diastolic properties of the left ventricle than through insufficient systolic performance. The most common symptom of idiopathic hypertrophic subaortic stenosis is dyspnea,1 while evidence of diminished systolic performance is meager. Likewise parts of the spectrum of coronary artery disease may present clinically with signs and symptoms related to increased left ventricular diastolic stiffness.2-3 Thus, a number of investigators have developed varying methods to evaluate the diastolic properties of the left ventricle in animal and man.4-7 These methods have generally lacked the frequent sampling of data necessary to accurately define the constantly changing relation between pressure and volume during diastole. In the present study, simultaneous left ventricular pressure and volume were sampled at 16.7 msec intervals in 17 patients. Data during diastole were examined with respect to the relation between pressure and volume, the shape of the diastolic pressure-volume curves, and the rates of change of ventricular volume relative to the pressure-volume information.

Methods

Diagnostic cardiac catheterization was performed in 13 patients. Thirteen patients (three normal, five coronary artery disease, two congestive cardiomyopathy, one idiopathic hypertrophic subaortic stenosis, one hypertensive heart disease, and one hypertrophic cardiomyopathy without obstruction) were studied during normal sinus rhythm. A second group of four patients had mitral stenosis and atrial fibrillation; one of these had modest aortic regurgitation.

Left Ventricular Volume Angiography

Left ventricular single plane cineangiography was
performed in the 35° right anterior oblique projection with the injection of 0.5 to 1 ml/kg of meglumine diatrizoate over a three to four second interval. Film was exposed at 60 frames per second. Left ventricular volume was calculated by the area-length method as described by Kasser and Kennedy. An XY digitizer and programmed calculator were used to determine left ventricular volume on sequential frames. The volume data was transferred to a PDP-9 computer and was smoothed according to a polynomial-approximation technique. Only angiograms of high quality were selected for study; premature ventricular contractions and beats immediately following a premature beat were excluded. This technique provides left ventricular volume data at 16.7 msec intervals. The rate of change of ventricular volume (dV/dt) was determined as the first derivative of the computed volume curve; the maximum filling rate during early diastole, max dV/dt, and the peak filling rate during atrial systole, peak (dV/dt)A, are tabulated in Table 1. Diagrammatic representations of the time-volume and dV/dt curves are shown in figure 1. The details of our methods are presented in a separate publication, and are essentially the same as those utilized by Hammermeister et

Figure 1

Diagrammatic representation of LV diastolic pressure, volume, rate of change of volume (dV/dt), and volume distensibility (dV/dP). The maximum rate of early diastolic filling, max dV/dt, and the peak rate of filling during atrial systole, (dV/dt)A, are identified by the arrows. LV volume distensibility, (dV/dP)A, is represented as a tangent to the diastolic pressure-volume curve at the onset of atrial systole. ES = end systolic; ED = end diastolic.

Table 1

<table>
<thead>
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<th>Left Ventricular Diastolic Pressure/Volume Data</th>
<th>LV volume (ml)</th>
<th>ED</th>
<th>P - maxV</th>
<th>X</th>
<th>Early diastolic slope (mmHg/10 ml)/sec</th>
<th>Peak (dV/dP)A</th>
<th>Atrial systole</th>
<th>Max dV/dt</th>
<th>LV dV/dt</th>
<th>LV PRESSURE</th>
<th>Diagnoses</th>
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Table 1

| Abbreviations: BSA = body surface area in m²; LV = left ventricle; ES = end systolic; VLP = volume at the lowest diastolic pressure; ED = end diastolic; LP = lowest diastolic pressure; P = pressure; V = volume; e = base of natural log; b and k are the values producing the best fit from the data; Max dV/dt = maximum rate of change of volume during early diastole; Peak (dV/dt)A = peak velocity of LV filling during atrial systole; AP = pressure difference between the best fit line and the point of maximum deviation from the line during atrial systole; (dV/dP)A = volume distensibility at the onset of atrial systole; HHDD = hypertensive heart disease; HCNO = hypertrophic cardiomyopathy-non obstructive; AI = aortic regurgitation; AFib = atrial fibrillation. |  }
al. in an extensive study of LV volume and rate of change of volume in man.\textsuperscript{11, 12}

Pressure Measurement

In seven cases a micromanometer\textsuperscript{*} was mounted on the tip of a \#8 NIH Angio catheter and a single catheter was used for the simultaneous recording of pressure and injection of contrast media. In ten cases a \#5 Millar mikro-tip catheter and a \#8 Pigtail catheter were positioned in the left ventricle for the simultaneous recording of pressure and injection of contrast media. The mikro-tip transducer was balanced and the gain adjusted to match a balanced Statham 23db external transducer before the mikro-tip catheter was introduced through a brachial arteriotomy. The accuracy of the micromanometer was verified by comparing the pressure with that obtained from a Statham 23db external gauge. In each case the two pressures were within 1 mm Hg during the middle one-third of diastole.

The high fidelity left ventricular pressure tracing plus the ECG and the injector marker signal were recorded at a paper speed of 200 mm per second during the left ventricular cineangiogram. The XY digitizer-calculator system was also used to digitize the left ventricular pressure at 16.7 msec intervals. End-diastolic pressure was identified and defined as the incisura on the left ventricular pressure pulse at end diastole. This point was observed at the junction of the A wave with the upstroke of the isovolumic pressure wave in patients with sinus rhythm and was found to range from 32–51 msec after the onset of the QRS complex. In patients with atrial fibrillation, end-diastolic pressure was taken at a point 40 msec after the onset of the QRS complex.

Matching of pressure and volume data throughout diastole was performed in the following manner. In seven cases a timing reference system, which marked the recording paper at the time of each cine exposure, was used. The measured exposure rate was 60 frames per second. At 50 cine exposure intervals a second identifying mark was recorded on the paper and a light emitting diode simultaneously marked the corresponding cine frame. Pressure was measured as stated above with the digitized samples being taken at the time of each cine exposure. The volume measurement used was the value taken from the smoothed volume curve, not from the individual raw volume data points. This method provides precise correlation between pressure and volume curves. Examination of the tabulated pressure-volume data from these seven cases demonstrated that the "maximum" or end-diastolic volume coincided within one frame with the end-diastolic pressure as defined above. With this justification, maximum volume was matched with end-diastolic pressure in the ten cases in which the timing reference system was not used, and with end-diastole as a reference, the preceding pressure-volume coordinates were matched. Errors in matching remain a potential problem in this type of study and would be expected to variably affect the absolute values of b, k, and \(\Delta P\) (see below).

Only data between the lowest diastolic pressure and end diastole were analyzed; when the lowest pressure in early diastole occupied more than one 16.7 msec interval, the last of these low points was selected as the lowest diastolic pressure. Pressure-volume data during very early diastole was excluded from analysis since this segment of early diastole was characterized by increasing volume and decreasing pressure and since the ventricle loses its exponential P-V relation at very low pressures.\textsuperscript{5, 6}

The exponential nature of the myocardial length-tension and ventricular pressure-volume relation has been previously emphasized.\textsuperscript{5, 13, 14} Accordingly, the relation between diastolic pressure and volume in the present study was assumed to be exponential and the sequential data were fitted by an exponential equation: \(P = be^{kV}\), where \(P = \text{pressure in mm Hg, } V = \text{volume in cc/m}^3\) of body surface area, \(e = \text{base of the natural log and } b \text{ and } k \text{ are the variables to be fitted to the data. All data points were equally weighted. Since there is no ideal manner to statistically compare these exponential data, comparison (of the fit of the equation) between the groups with normal sinus rhythm and the group with mitral stenosis was made primarily by visual inspection of the P-V plots. A variance ratio test\textsuperscript{15} was also utilized.}

Pressure differences (\(\Delta P\)) between the best fit diastolic P-V line and the P-V coordinates during atrial systole were measured at the point of maximum pressure deviation from the line. Volume distensibility (\(dV/dP = 1/kP\)) may be estimated at any given operating pressure (i.e., pressure at the onset of atrial systole, end-diastolic pressure, etc.) if a value for \(k\) can be determined.\textsuperscript{6, 14} Volume distensibility at the onset of atrial systole, (\(dV/dP)_s\), was calculated in each case from the best fit value for \(k\) and the pressure at the onset of atrial systole (fig. 1).

The nature of the investigative portion of the catheterization procedure was discussed with each patient and his informed consent was obtained prior to the study. The procedure was uncomplicated in all 17 patients.

Results

The clinical diagnosis and the pertinent hemodynamic data are shown in table 1 and figures 2 through 6. The diastolic pressure-volume data were analyzed only during the period between the lowest diastolic pressure and end diastole (see Methods).

Pressure-Volume Relations

In each case, the relation between pressure and volume appeared curvilinear and the data were fitted by an exponential equation (\(P = be^{kV}\)) as described in the Methods section. The fit of the equation to the data obtained from patients with mitral stenosis and atrial fibrillation (figs. 3, 5) appeared better (by visual inspection and variance ratio test) than the fit to the data from patients in normal sinus rhythm (figs. 2, 4, and 5). Examination of the relationship of the diastolic pressure-volume data in the patients with sinus rhythm reveals higher pressure during atrial systole than would be predicted from the exponential relation, which is approximated by the best fit line (figs. 2, 4, and 5). The difference (\(\Delta P\) in mm Hg) between the best fit line and the pressure at the point of maximum deviation during atrial systole ranged from +0.9 mm Hg to +4.8 mm Hg (table 1 and fig. 6). The difference between the left ventricular end-diastolic pressure and the best fit line ranged from −0.5 mm Hg to +1.4 mm Hg; in only one case did the end-diastolic

\textsuperscript{*}mikro-tip, Millar Instr., Inc.
pressure deviate from the best fit line more than the worst-fitting point obtained during atrial systole (pt. #1). In each of the four patients with mitral stenosis and atrial fibrillation, the relation between pressure and volume was smooth, without consistent deviations from the best fit line (figs. 3 and 5).

The values for the rate variable \( k \) in the exponential equation fell in the general range of those previously found using different methods. The highest \( k \) was obtained from a patient with hypertrophic cardiomyopathy (pt. 6, IHSS) and the lowest values for \( k \) were found in larger dilated hearts (pts. 4 and 14) while the values for \( k \) in the patients with normal left ventricles were intermediate. The average value for the pressure intercept (b) in this group of patients was 0.68 mm Hg (range 0.01 to 3.6).

**Maximum Ventricular Filling Rate**

The maximum rate of LV filling in patients 1 through 5 (normal and cardiomyopathy) ranged from 260 to 370 cc/m²/sec; these filling rates and the overlap between normal and cardiomyopathy are in agreement with the data of Hammermeister and Warbasse.11 Left ventricular maximum filling rates in our four patients with mitral stenosis ranged from 215 to 270 cc/m²/sec and in the five patients with CAD from 197 to 290 cc/m²/sec; maximum filling rates in the three with LVH also appeared to be less than normal (range 213 to 255 cc/m²/sec). Except for our patients with LVH, these data are consistent with those reported by Hammermeister and Warbasse; in their study the maximum filling rates in LVH (aortic stenosis and IHSS) did not differ significantly from the normal group.

**Atrial Systole**

Peak rates of filling during atrial systole ranged widely and a trend toward a difference between the various groups was not apparent (table I and fig. 6). This data is likewise in agreement with the studies of Hammermeister and Warbasse. As is shown in figure 6, the lowest values for \((dV/dt)_A\) were found in the patients with reduced values for \((dV/dP)_A\) while higher values for \((dV/dt)_A\) were determined in patients with higher values for \((dV/dP)_A\). The relation between LV distensibility at the onset of atrial systole and the pressure deviation \((\Delta P)\) from the best fit line is
Diastolic pressure-volume relations in three patients with coronary artery disease (above) and in three patients with mitral stenosis and atrial fibrillation (below). Data during atrial systole tends to fall above the best fit in CAD while data in MS does not show consistent departure from the best fit line.

Likewise shown in figure 6; it appears that higher values for ΔP are found in less distensible ventricles.

Discussion

Remington and Alexander have discussed viscoelastic properties of heart muscle and have suggested that at faster rates of stretch, viscous drag produces departures from simple elastic behavior and that faster rates of stretch are associated with higher tensions for a given length. On the basis of studies in the isolated left ventricle and in the conscious animal, several investigators have concluded that the LV diastolic pressure-volume or pressure-dimension relations are influenced by dynamic mechanical properties such as inertia and viscosity. It would thus seem that variable rates of change of volume during diastole might contribute to the scatter of pressure-volume data and might result in alterations in the relation between pressure and volume separate from those determined by the elastic properties of the muscle.

In the present study, instantaneous diastolic pressure-volume data from 17 patients were fitted by an exponential equation, and a best fit line for the data was obtained in each case. Excessive pressure (relative to the best fit line) was found during early atrial systole in patients with normal sinus rhythm (figs. 2, 4, and 5). This excess pressure relative to volume is analogous to the higher tensions for a given length which are observed during faster rates of stretch of isolated muscle and thus, may reflect viscous properties of the diastolic LV. Attenuation of variable rates of filling in patients with mitral stenosis and atrial fibrillation was associated with less scatter of the P-V data and with no consistent deviations from the best fit line (figs. 3 and 5). It would therefore appear that partial obstruction to left ventricular filling (mitral stenosis), in combination with an absent atrial contraction (atrial fibrillation), results in slow uniform filling and thus, the basic elastic (exponential) relation between P and V is not obscured by factors related to dynamic influences.

If viscosity is responsible for the observed deviations (ΔP during atrial systole) from the best fit pressure-volume line, then these deviations should be velocity dependent. Because only a single observation was made in each patient, only one coordinate of ΔP versus (dV/dt)A is available, and thus, an over-all relationship between ΔP and velocity in the individual patient remains speculative. However, as is shown in figure 6, lower values for distensibility, (dV/dP)A, are associated with reduced rates of filling (during atrial systole) and high values for ΔP, while higher values for (dV/dP)A are associated with faster rates of filling and a low ΔP. Thus, it seems that a family of curves may exist in which the velocity dependence of ΔP is modified by the volume distensibility of the ventricle. In the panel on the right (fig.
6), ΔP is plotted against peak (dV/dt)ₘ for all 17 patients.

In this study, the relation between pressure and volume throughout diastole is characterized by the rate variable (k) in the equation P = beᵏV; distensibility (dV/dP) at a given LV pressure has been defined as the slope of a tangent to the curve at the given pressure.⁶, ¹⁶, ¹⁸ If diastolic pressure-volume data is displaced from the elastic or exponential curve by viscous or other dynamic influences, errors may be introduced in the estimation of distensibility or compliance. However, the values for k found in the present study are in the general range of those previously reported using a single end-diastolic pressure-volume coordinate and a fixed intercept (b) at zero volume.⁶, ¹⁶ The highest values for k are found in small ventricles with elevated filling pressures and the lowest values are found in large dilated hearts. Thus k may represent an index or coefficient of volume elasticity in the intact ventricle, but comparison of myocardial stiffness between patients may be precluded by the lack of a normalization factor.

The use of single plane cineangiography for determination of left ventricular volume in patients with coronary artery disease and asynergy as well as in patients with IHSS can have important limitations, but because this study involves mid to late diastolic volume data, the hazards of single plane angiography are, to some extent, diminished. Late systolic volume data may be highly inaccurate in these situations but systole was not analyzed in the present study. Agreement between our data and those reported by others¹¹ supports the accuracy of the methods utilized herein.

As expected, low filling rates were found in mitral stenosis; in some patients with CAD or LVH, maximum filling rate was likewise reduced. The single patient with IHSS had a maximum LV filling rate which was in the range of the group with mitral stenosis. A reduced filling rate in IHSS explains, at least in part, the observations of Stewart et al.²¹ on the slow y descent of the left atrial pressure and of Quinones et al.¹⁸ on the reduced E to F descent of the mitral valve echogram. Depressed early diastolic maximum filling rates in some patients with reduced diastolic compliance (CAD or LVH) have previously been suggested as a common denominator of the reduced E to F descent of the mitral valve echogram. Maximum filling rate generally occurred at or slightly before the “lowest diastolic pressure” in the patients with normal sinus rhythm. This finding correlates with the observations of Porter et al. who found that the maximum filling rate nearly coincided with the lowest pressure or wall stress.²₂ These authors found a positive correlation between maximum filling rate and the P-V relation during early diastole; estimation of early diastolic distensibility was not attempted in the present study since pressure is falling and volume is increasing during this period of the cardiac cycle, and since the ventricle loses its exponential P-V relation at very low pressures.⁵, ⁶ Since dV/dt is maximum in very early diastole, viscous effects may be in part responsible for the observation that pressure is higher than would be predicted from the volume. The relative contribution of incomplete ventricular relaxation to this phenomenon likewise remains undefined.

Based on a reduction in end-diastolic pressure associated with an increase in end-diastolic volume in patients with IHSS treated with practolol, Webb-Peploe has suggested that this beta-receptor blocking agent causes an increase in the compliance of the hypertrophic left ventricle.²³ Likewise, Leachman has shown a reduction in left ventricular end-diastolic pressure in patients with IHSS treated with mitral valve replacement.²⁴ Since it would seem unlikely that these already small ventricles could undergo further reduction in volume, he has speculated that increased left ventricular compliance follows mitral valve replacement. In the light of data reported herein, it would seem possible that changes in the rates of filling (as might occur with beta blockade or the imposition of a mitral prosthesis) could result in a reduction in the manifestations of dynamic properties of the diastolic ventricle; thus a lower end-diastolic pressure with no decrease in ventricular volume could be explained without postulating an alteration in the elastic properties of the diastolic left ventricle. Other mechanisms, such as a change in ventricular diastolic geometry, altered left atrial systolic performance, a reduction in heart rate, or even a change in the P-R interval, might also be responsible, in part, for these observations.

Left ventricular diastolic pressure-volume curves are complex and are not simply mono-exponential. Determinants of the P-V relations include not only the basic elastic properties of the ventricle and to some extent the process of myocardial relaxation, but it also appears that dynamic factors such as viscous drag also influence these relations. The relative contributions of these factors on estimates of diastolic compliance and on calculations of diastolic stress-strain relations remains unknown, but dynamic properties during filling may preclude the assumption of a simple exponential relation between pressure and volume throughout diastole.

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