Acute Hemodynamic Interventions Shift the Diastolic Pressure-Volume Curve in Man

EDWIN L. ALDERMAN, M.D., AND STANTON A. GLANTZ, PH.D.

With the Technical Assistance of Sherilyn C. Robison

SUMMARY Frame-by-frame analysis of angiograms in 16 patients revealed that hemodynamic interventions are capable of producing substantial shifts in the diastolic pressure-volume curve. Angiotensin raises blood pressure and shifts the entire pressure-volume curve up, and nitroprusside lowers blood pressure and shifts the curve down. Indirect measurements of pleural pressure in seven patients (via esophageal pressure) showed that pleural pressure changes were too small to account for these shifts. Analyzing our results in terms of a theoretical pressure-volume equation previously validated in dog studies did not show the observed shifts to be the product of acute changes in the elasticity of the myocardium itself. This same analysis suggested that indirect changes in the external mechanical constraints acting on the left ventricle such as the right ventricular pressure, the pericardium, and perhaps viscoelastic effects related to changes in filling rate account for the pressure-volume curve shifts with intervention. The fact that one cannot in general relate a specific volume to a given pressure in the face of hemodynamic interventions calls into question the use of end-diastolic pressure interchangeably with end-diastolic fiber length when interpreting systolic events in terms of the Frank-Starling mechanism.

DURING DIASTOLE the left ventricle fills passively, with its pressure and volume related by a curve which reflects both ventricular geometry and the elasticity or stiffness of cardiac muscle. One generally describes the passive elasticity of cardiac muscle by means of an exponential curve relating stress (force/area) to strain (percentage distension), with the muscle becoming stiffer as it is stretched. The pressure-volume relationship has been assumed to be sufficiently constant over the short term to use left ventricular end-diastolic pressure interchangeably with end-diastolic circumferential fiber length in analyses of ventricular function based on the Frank-Starling mechanism. Chronic cardiac disease may cause the ventricle to dilate or hypertrophy, and these geometric changes distort its diastolic pressure-volume relationship. In addition, disease might change the passive elasticity of the myocardium itself, altering the pressure-volume relationship. In an acute situation, however, it is assumed that hemodynamic interventions simply move the ventricle up and down the same pressure-volume curve. This assumption is based on the fact that no agents are known to affect passive elasticity of normally oxygenated papillary muscle, and the fact that the ventricle cannot actually become hypertrophied.

We explored this assumption of constancy of the pressure-volume relationship by measuring diastolic pressure-volume curves based on frame-by-frame analysis of angiograms in 16 patients. Acute interventions with nitroprusside and angiotensin usually noticeably shifted the diastolic pressure-volume curve. This result brings into question the assumption that the diastolic pressure-volume relationship remains constant despite altered hemodynamic circumstances, an assumption which underlies the use of filling pressures as a substitute for diastolic circumferential fiber length in analyses of ventricular systolic function.

Methods

Theoretical Considerations

In order to calculate myocardial stiffness from pressure and volume data obtained in the intact ventricle, two equations relating pressure-volume measurements to myocardial stiffness have been used, one empirical and one theoretical. The pressure-volume curve exhibits an upward curvature which has led to its being characterized with the empirical exponential equation

\[ p = A e^{Bv} \]  

in which \( p \) and \( V \) equal diastolic pressure and volume, and \( A \) and \( B \) are empirical constants. These constants change value with changes in the pressure-volume curve but cannot be related theoretically to stress, strain, or stiffness of the myocardium itself.

Recently, Glantz and Kernoff derived a theoretical equation which defines the pressure-volume curve in terms of the ventricle’s volume, average wall thickness, and the muscle’s exponential stress-strain curve. This equation follows from five assumptions about the left ventricle:

1) The left ventricle behaves as a spherical shell of uniform thickness which fills passively, i.e., the myocardium is not contracting.
2) All the muscle fibers carry the average stress and deform as if at midwall.
3) It remains in static equilibrium.
4) Internal pressure induces the only load. The effects of right ventricular and pleural pressures are not included.
5) Unstimulated muscle may be characterized by a parallel elastic element model which behaves elastically under a one-dimensional load according to

\[ \sigma(x) = \alpha \left[ e^{\beta x} - 1 \right] \]

in which \( \sigma \) = stress (force/area), \( x \) = loaded muscle length, \( x^* \) = rest length (where \( \sigma = 0 \)), and \( \alpha \) and \( \beta \) are elastic constants.

The Appendix shows that these assumptions lead to the theoretical pressure-volume equation

\[ p = c \eta (2 + \eta) \left( e^{2 \eta/3V + \eta} \right)^{3/2V} - 1 \]

where \( \eta = h \sqrt{4\pi/3V} \).
and $p$, $V$, and $h$ equal ventricular pressure, volume, and mean diastolic wall thickness, respectively. The parameters $\alpha$ and $\beta$ describe the muscle's nonlinear elasticity and $x^*$ equals half the circumference of the sphere defined by the midwall when there is no pressure difference across the wall.

Glantz and Kernoff validated equation [2] by first measuring pressure-volume curves in excised dog ventricles and calculating values of the parameter $\beta$, which characterizes muscle's nonlinear elasticity. Next, they measured one-dimensional stress-strain curves for muscle strips removed from the ventricles and fit the results to the stress-strain equation in assumption 5. After normalizing $\beta$ for differences in specimen length, they found no significant difference between the values of this stiffness parameter calculated from the intact ventricles and the values calculated from the muscle strips.

We computed the parameters $A$ and $B$ in equation [1] by converting it to the form

$$\ln p = \ln A + BV$$

and using the linear least-squares technique. The parameters $\alpha$, $\beta$, and $x^*$ in equation [2] were computed using a nonlinear least-squares technique based on Brent's PRAXIS algorithm, with two or three different first guesses being provided to ensure that the algorithm found the best fit. Theoretical and numerical analyses revealed computation of $\alpha$ to be relatively noisy, but $\beta$ and $x^*$ were accurate to two significant digits. Therefore, we present all results to two significant digits.

**Ventricular Volume**

Patients consenting to participate in this protocol were studied during diagnostic cardiac catheterization. We included 16 patients in our analysis (tables 1 and 2) after excluding those with significant segmental wall motion abnormalities or inadequate ventricular visualization. One patient had mitral valve prolapse without mitral regurgitation, one had mitral stenosis, five had significant mitral regurgitation, five had aortic regurgitation, two were found to be normal and four had coronary artery disease without segmental wall motion abnormalities. After instructing patients to maintain full end-inspiratory effort, we administered 50 ml contrast through a #6.7 French pigtail catheter over a three-second period. A single-plane cesium iodide image intensifier system in the 30° right anterior oblique projection and a video disc were used to record the ventriculograms. A light-pen computer system, which calculates single-plane volumes using Sandler and Dodge's arealength method, was used to analyze ventricular volume every 33 msec (30 frames/sec). We corrected for magnification by measuring left ventricular height above the table top echographically and used a fixed distance between the image intensifier and table top. The earliest adequately visualized two beats in patients with sinus rhythm, or four beats in those with atrial fibrillation, were traced. Diastolic frames were drawn in duplicate and averaged. Beats following extrasystoles or postextrasystolic beats were excluded. The electrocardiographic R wave, recorded synchronously with the ventriculogram on the video disc, was used to average volume measurements from different cardiac cycles at equivalent times following the R wave. In nine of the 16 patients we were able to directly measure left ventricular diastolic wall thickness along the lateral wall on one or more frames and used the average value of these measurements as the constant wall thickness, $h$, in equation [2]. In the remaining seven patients we assumed $h = 1.0$ cm.

**Ventricular Pressure**

We recorded ventricular pressure, zeroed at the mid-chest level, just prior to the ventriculogram with the patient in the right anterior oblique projection during a full-held inspiratory effort. A Micron MP-15 transducer was connected via a wide bore manifold to the same #6.7 French pigtail catheter used for the ventriculogram. Bench testing showed that the exclusion of connecting tubing and the particular combination of manifold and small volume displacement transducer provided a flat frequency response to 14 Hz. This system eliminated 90% of the resonance artifacts which produce the initial diastolic undershoot and subsequent oscillations commonly seen on the diastolic pressure tracings. The filter, used to eliminate high frequency artifact, induced a 40 msec phase lag of pressure signal. To help compensate for the phase lag of the filter, we aligned the pressure and volume data on the basis of the R waves and then shifted the angiographic data by one frame (33 msec). In four patients a #8 Millar micromanometer-tipped angiographic catheter provided pressure and volume measurements, with both being recorded simultaneously on the video disc for light-pen computer analysis. In these patients, analysis of pressures and volumes was done only on cardiac cycles following completion of the contrast injection because of an artifactual downward displacement of the ventricular pressure due to the pressure of the contrast injection on the catheter air tube. Analysis of pressure-volume points was initiated at the minimum of the diastolic pressure tracing and terminated at the peak of the left ventricular A wave.

Twenty minutes after recording control pressure and volume data, we infused nitroprusside in seven patients, beginning with 15 $\mu$g/min and increasing by 10–15 $\mu$g/min every two minutes until the mean aortic pressure dropped 20 mm Hg. We infused angiotensin in eight patients, beginning at 0.4 $\mu$g/min and increasing by 0.4 $\mu$g/min every two minutes until mean aortic pressure increased 25 mm Hg. During intervention we again measured the diastolic pressures and volumes. To study the reproducibility of pressure-volume curves, we administered a slow infusion of 5% dextrose and water (less than 100 cc) instead of drug to three patients during the 30 min interval between two sequential ventriculograms.

**Esophageal Pressure**

In order to estimate pleural pressure at end-held inspiration (same as during ventriculography), we measured esophageal pressure in seven additional patients through a #14 fluid-filled pediatric feeding tube positioned radiographically in the esophagus behind the left atrium. Pressure was then zeroed at the level of the catheter tip by using an electrocardiogram to measure the depth of the posterior left atrial wall while the subject was in the right anterior oblique position. Daily and Bondurant have measured esophageal pressure and pleural pressure directly. Their data demonstrate
that esophageal pressure will estimate pleural pressure to one significant digit. Ventriculograms were not performed during these esophageal pressure measurements, which were repeated one to three times to study the absolute level and reproducibility of end-inspiratory pleural pressures.

### Results

**Reproducibility**

Before studying how interventions which significantly alter hemodynamics change the pressure-volume relationship, one must assess the reproducibility of these measurements. The pleural pressure is an important factor in determining the pressure-volume curve, for it determines the true pressure gradient across the left ventricular free wall. During active inspiration the pressure generally dropped to −10 mm Hg, then slowly increased to a repeatable steady-state while inspiration was maintained. Table 3 shows that, while the value of pleural pressure at end-held inspiration is reasonably repeatable, it varied widely from patient to patient. This repeatability of pleural pressures within each patient makes it possible to compare a patient with himself (i.e., before and after an intervention). The fact that most of the pleural pressures reported at the end of sustained full-held inspiration were positive reflected the tendency for patients to perform a partial Valsalva maneuver, despite instructions to the contrary.

To test the repeatability of pressure-volume measurements, three subjects had sequential ventriculograms performed 30 min apart, with virtually identical ventricular pressures and heart rates during both studies. Figure 1 shows the raw data on ventricular pressure and volume measure-
A previous systole, so the assumption of complete relaxation used in deriving equation [2] does not hold. Therefore, we analyzed the diastolic pressure-volume curve from the minimum diastolic pressure to the ventricular A wave peak.

Table 2. Results of Ventricular Elasticity Measurements

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>A</td>
<td>B</td>
<td>r</td>
</tr>
<tr>
<td>Control (dextrose and water) (N = 9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>C</td>
<td>170</td>
<td>10</td>
<td>.63</td>
<td>3.8</td>
<td>.011</td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>240</td>
<td>9</td>
<td>6.2</td>
<td>.009</td>
<td>.97</td>
</tr>
<tr>
<td>2</td>
<td>C</td>
<td>230</td>
<td>8</td>
<td>.83</td>
<td>2.1</td>
<td>.014</td>
</tr>
<tr>
<td>3</td>
<td>C</td>
<td>160</td>
<td>7</td>
<td>.69</td>
<td>.015</td>
<td>.71</td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>180</td>
<td>7</td>
<td></td>
<td>.12</td>
<td>.053</td>
</tr>
<tr>
<td>Nitroprusside (N = 7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>C</td>
<td>180</td>
<td>14</td>
<td>1.0</td>
<td>3.0</td>
<td>.0079</td>
</tr>
<tr>
<td></td>
<td>NTNP</td>
<td>240</td>
<td>4</td>
<td>.0016</td>
<td>.047</td>
<td>.94</td>
</tr>
<tr>
<td>5</td>
<td>C</td>
<td>120</td>
<td>10</td>
<td>1.0</td>
<td>.50</td>
<td>.013</td>
</tr>
<tr>
<td></td>
<td>NTNP</td>
<td>200</td>
<td>11</td>
<td>1.7</td>
<td>.0095</td>
<td>.98</td>
</tr>
<tr>
<td>6</td>
<td>C</td>
<td>320</td>
<td>6</td>
<td>.96</td>
<td>.48</td>
<td>.024</td>
</tr>
<tr>
<td></td>
<td>NTNP</td>
<td>60</td>
<td>8</td>
<td>.021</td>
<td>.042</td>
<td>.99</td>
</tr>
<tr>
<td>7</td>
<td>C</td>
<td>120</td>
<td>7</td>
<td>1.0</td>
<td>.00015</td>
<td>.056</td>
</tr>
<tr>
<td></td>
<td>NTNP</td>
<td>110</td>
<td>9</td>
<td>.0023</td>
<td>.050</td>
<td>.99</td>
</tr>
<tr>
<td>8</td>
<td>C</td>
<td>90</td>
<td>11</td>
<td>.75</td>
<td>.027</td>
<td>.085</td>
</tr>
<tr>
<td></td>
<td>NTNP</td>
<td>95</td>
<td>5</td>
<td>.022</td>
<td>.095</td>
<td>.98</td>
</tr>
<tr>
<td>9</td>
<td>C</td>
<td>60</td>
<td>13</td>
<td>1.0</td>
<td>2.0</td>
<td>.020</td>
</tr>
<tr>
<td></td>
<td>NTNP</td>
<td>140</td>
<td>10</td>
<td>1.0</td>
<td>.022</td>
<td>.91</td>
</tr>
<tr>
<td>10</td>
<td>C</td>
<td>170</td>
<td>12</td>
<td>.70</td>
<td>.13</td>
<td>.039</td>
</tr>
<tr>
<td></td>
<td>NTNP</td>
<td>120</td>
<td>9</td>
<td>.13</td>
<td>.042</td>
<td>.91</td>
</tr>
<tr>
<td>Mean C</td>
<td></td>
<td>151</td>
<td>10.4</td>
<td>.92</td>
<td>.035</td>
<td>.93</td>
</tr>
<tr>
<td>Mean NTNP</td>
<td>137</td>
<td>7.4</td>
<td>.41</td>
<td>.044</td>
<td>.96</td>
<td>44000</td>
</tr>
</tbody>
</table>

Table 3. Steady-state Esophageal Pressures at End-held Inspiration

<table>
<thead>
<tr>
<th>Pt / Age/Sex</th>
<th>Dx</th>
<th>Pressure Measurements (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/62/M</td>
<td>CMP</td>
<td>First</td>
</tr>
<tr>
<td>2/64/F</td>
<td>CMP</td>
<td>-2</td>
</tr>
<tr>
<td>3/62/RHD</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>4/63/CAD</td>
<td>6</td>
<td>-</td>
</tr>
<tr>
<td>5/35/NL</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>6/56/RHD</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>7/59/M</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

Abbreviations: Dx = diagnosis; CMP = cardiomyopathy; CAD = coronary artery disease; RHD = rheumatic heart disease (mixed mitral disease); NL = normal.
Comparison of Empirical and Theoretical Equations

The diastolic pressure-volume relationships of all 16 individuals curved upward as volume increased. The empirical exponential relationship (equation [1]) described the data with correlation coefficients ranging from 0.65 to 0.99 (mean, 0.90). The parameter B, which describes the pressure-volume curve's steepness and curvature, increased as the curve steepened. In the three control patients in whom duplicate studies were done, the B value calculated for the second study varied −52% to +23% from the initial study (fig. 2, table 2). The theoretical pressure-volume equation [2] described the data of the 16 patients with significantly better \( P < 0.02 \) correlation coefficients (0.55 to 1.0, mean 0.90) than those obtained using the empirical equation. In the three control patients, the β values calculated from the duplicate study varied −25% to +12% from the initial study (table 2), which is about one-half the variation of parameter B in the empirical equation. The β value calculated by means of the theoretical equation better fits the data and reflects the nonlinear elastic stiffness of the myocardium itself.

In nine of the ten patients in sinus rhythm, pressures obtained on the ventricular A wave upstroke exceeded the curve predicted by both the empirical and theoretical equations (fig. 3A). In contrast, points for patients in atrial fibrillation fell near the predicted curve derived throughout diastole (fig. 3B). These augmented pressures during the A wave, when the filling rate suddenly increases, suggest that viscous effects, neglected in our analysis, may play an important role during the A wave. Therefore, pressure-volume curves derived entirely from A wave data will appear steeper than curves obtained entirely from pre-A wave data. To obtain the maximum number of points along the pressure-volume curve, we included A wave data; however, only two patients were in sinus rhythm with heart rates over 90 beats/min, a situation which would weight the data more heavily with pressure-volume points derived from atrial systole.

Intervention Effects

Noble et al. used permanently implanted radiopaque markers to show that volume loading and pacing caused the
ventricles in the conscious dog to move up the same diastolic pressure-volume curve. This result is consistent with the view, expressed in our five assumptions, that during diastole the ventricular pressure-volume curve is a manifestation of passive elastic forces that arise in the myocardium. We used nitroprusside and angiotensin to obtain analogous data in man. Nitroprusside administered to seven patients decreased left ventricular end-diastolic pressure by a mean of 43% and end-diastolic volume by 15% (table 1). Angiotensin administered to eight patients increased end-diastolic pressure by 74% and end-diastolic volume by 12%. If the diastolic pressure-volume curve is entirely a manifestation of passive elastic forces arising within the myocardium, then the pressure-volume data during control, nitroprusside, and angiotensin conditions should fall along a single curve. Pressure-volume data derived from diastoles at rest or during interventions may reflect a single pressure-volume curve in four of seven nitroprusside studies and in one of eight angiotensin studies. This is defined as pressures within 5 mm Hg of one another at the same volumes for at least 50% of the points where the two curves overlap. Figure 4 illustrates the results in two of these patients and suggests that, although nitroprusside or angiotensin changed the observed pressures and volumes from control, the individual data points appear to fit along a single pressure-volume curve.

Figure 5 illustrates the more usual situation in which the pressure-volume curve shifts noticeably upward with angiotensin, and downward during nitroprusside infusion. Angiotensin produced greater shifts than nitroprusside, reflecting its more powerful hemodynamic effects, particularly in patients with aortic regurgitation, and reflecting the fact that the ventricle becomes stiffer at higher volumes (i.e., the nonlinear nature of the pressure-volume curve). These shifts exceeded the small changes in intraventricular pressure that result from pleural pressure variations due to inspiratory effort. Following interventions, the pressure-volume curves did shift noticeably for most patients. However, the two parameters which most reliably (from a computational standpoint) characterize the passive elasticity of the myocardium itself, \( \beta \) and \( x^* \), did not change significantly (fig. 6).

Discussion

If the intact left ventricle behaved as an unconstrained purely elastic shell, all pressure-volume points would fall on the same curve, regardless of how one altered filling pressures acutely. This behavior was observed by Diamond et al.\(^{19}\) and by Glantz and Kernoff\(^{14}\) in excised ventricles, and by Noble et al.\(^{18}\) using permanently implanted radiopaque markers in conscious dogs. Neither nitroprusside nor angiotensin are known to affect the passive elasticity of normally oxygenated cardiac muscle. Yet, nitroprusside and angiotensin interventions generally induced marked changes in diastolic pressure-volume curves. Although nitroprusside may reverse increases in resting stiffness provoked by hypoxia,\(^{20}\) there was no evidence of active ischemia in the few patients in this series who had coronary artery disease. We have also reported downward shifts of pressure-volume curves following propranolol administration in patients with...
impaired systolic function. One could argue that direct or reflex changes in sympathetically mediated autonomic tone alter myocardial passive elasticity; however, catecholamines do not affect the passive elasticity of papillary muscles.

The shifts we observed in pressure-volume curves following interventions far exceeded the variability observed in the three control patients. The duplicate control pressure-volume curves reflected only minor changes in filling pressure, probably due to variation in inspiratory effort, and hence pleural pressure. Angiotensin produced prominent pressure-volume curve shifts, irrespective of whether control diastolic pressures and volumes were normal or abnormal. Nitroprusside tended to shift the pressure-volume curves downward, most prominently in individuals with elevated control pressures and volumes. These observations are similar to those reported for nitroprusside by Grossman et al.

The reproducibility studies demonstrated that although changes in pleural pressure can affect pressure-volume curves between patients, each patient generally maintains the same level of full inspiratory effort, i.e., pleural pressure. When ventricular filling pressures are low, pleural pressure differences between patients may be large enough (up to 10 mm Hg difference noted in this study) to prevent quantitative comparison of computed elasticity parameters between patients. The fact that variation in pleural pressure may be of the same order of magnitude as normal diastolic pressures makes it difficult to quantitatively compare diastolic pressure-volume curves from different patients in whom the pleural pressures are not known. In our intervention studies, however, quantitative analysis is possible, because pleural pressure remains constant within each patient. More important, pleural pressure changes in a given patient are not of sufficient magnitude to produce the shifts we observed in the pressure-volume curves.

The observation of augmented pressures during the A wave, when the filling rate increases, suggests that viscous effects, which we have neglected in our analysis, may play an important role during atrial systole. Certainly, pressure-volume relationships based on A wave data alone, particularly following interventions which might affect the rate of ventricular filling during atrial systole, may be dominated by viscous effects. Horowitz and Bishop in canine studies, noted changes in the diastolic pressure-volume curve following isoproterenol and metaraminol infusions, which they attributed to viscous or inertial forces. In contrast, our data show that the mean rate of diastolic filling from the time of the minimum diastolic pressure to the A wave peak (ΔV/Δt, table 1) was generally unaffected by interventions and suggest that altered viscous forces are not responsible for the observed shifts of pressure-volume curves.

Close examination of table 2 shows that, while not a significant trend, β increases more often than not following angiotensin and decreases more often than not with nitroprusside. The variation in β reflects, in part, the limitations of pressure and volume measurements not made with manometer-tipped catheters and single plane angiography. Our use of a tuned catheter system and the exclusion of patients with nonuniform wall motion minimizes these difficulties. The major cause for the β variation between patients and between interventions is the numerical difficulty in quantitating the entire nonlinear pressure-volume curve using short segments. At higher pressures the pressure-volume curve is steeper and this fact leads the computer to select higher values of β than it would if it had the entire curve. For example, the data from both patients in figure 4 clearly fall along a single pressure-volume curve, yet the values of β, which produce the closest agreement (by least-squares) between the data and equation 2 vary markedly, depending on whether one uses the control points or intervention points. Since angiotensin increases pressure and nitroprusside decreases it, we obtain different segments of the pressure-volume curve which would tend to make β look larger than it is with angiotensin and smaller with nitroprusside. Thus, the tendency toward a pattern in β's behavior with intervention is most likely a computational artifact. In any event, it is not statistically significant. Similar problems arise when using equation 1. Control and intervention data were always handled separately.

Large changes in the computed value of α accompanied the interventions, and probably accounted for much of the shift in the pressure-volume curves. Previous analysis of the data of Diamond et al., taken from excised dog ventricles clamped in different ways, suggests that in equation 2 external mechanical forces applied to the ventricle produce large changes in α, whereas the values of β and x do not change significantly. This fact suggests searching for external mechanical constraints on the left ventricle to explain the pressure-volume curve shifts following interventions. Our analysis neglects three possible mechanical constraints on the left ventricle: pleural pressure, right ventricular pressure, and the pericardium. The importance of pleural pressure in considering shifts in pressure-volume curves during interventions and in comparing different patients has already been discussed.
Intervention-induced changes in right ventricular diastolic pressure may play an important role in determining the observed shift in the pressure-volume curves. Bemis et al.\textsuperscript{28} and Elzinga\textsuperscript{29} used isolated perfused hearts with intact pericardia to show that increases in right ventricular filling pressure increased left ventricular filling pressure and altered its geometry. From a mechanical point of view this result is quite reasonable, since the stresses in the septum, which partially define the left ventricular pressure-volume curve, depend upon the pressure gradient across it. In our data, nitroprusside decreased not only mean aortic pressure and left ventricular filling pressure but also right ventricular diastolic pressure (Table 1). Thus, the results of Bemis et al. and Elzinga lead one to predict that this intervention would produce a greater drop in pressure at a given volume than one would expect if the left ventricle behaved as an unconstrained body subject to uniform pressure loads. In short, their results anticipate our observed downward shift in the pressure-volume curve with nitroprusside. Conversely, angiotensin would increase right ventricular pressure and hence shift the left ventricular pressure-volume curve upward (higher pressure at a given volume). This upward shift was, however, much greater than the downward shift that accompanied nitroprusside, even allowing for the more marked hemodynamic changes induced by angiotensin.

We are left with the problem of explaining why the data of Noble et al.\textsuperscript{18} in the intact canine ventricle indicate that the left ventricle exhibits a unique pressure-volume curve, even in the presence of interventions which probably increased right ventricular diastolic filling pressures. The fundamental difference between the present work and these earlier studies is the fact that earlier experimental studies were carried out on excised ventricles without pericardia,\textsuperscript{4, 19} or on intact conscious dogs whose pericardia had been severed for surgical implantation of radiopaque markers.\textsuperscript{18} Thus, in these studies the pericardium did not restrict left ventricular expansion. In contrast, our patients had intact pericardia, so that interventions which caused substantial volume increases may make the ventricle press against the stiff pericardium,\textsuperscript{27} thereby giving rise to larger pressure increases than one would expect from the pressure-volume relationship of an unrestricted ventricle. A study by Spotnitz and Kaiser in canine ventricles does show altered pressure-volume curves following pericardial excision.\textsuperscript{25}

If, indeed, the pericardium does impose external mechanical loading on the left ventricle, it is possible that in situations of relatively subacute or acute left ventricular decompensation, the pericardium will not have had time to accommodate to the increased left ventricular volumes. In this clinical setting, interventions which decrease left ventricular volume may lower associated pressures to a greater extent than one would predict using a single pressure-volume curve, by virtue of relief of the restrictive action of the pericardium. Conversely, interventions which acutely elevate end-diastolic volumes may yield higher filling pressures than are consistent with a single pressure-volume curve, because of mechanical constraint imposed by the pericardium.

**Figure 7.** (Left) A simple description of the left ventricular pressure-volume relationship embodied in the five simplifying assumptions used to derive the theoretical equation [2] is shown. The ventricle is assumed to be an unconstrained elastic sphere that fills passively. Below) A more realistic and detailed description of the factors which determine the pressure-volume relationship on a beat-to-beat basis is shown. Systolic performance is included to indicate some of the feedback loops which impinge upon the diastolic pressure-volume relationship.
Conclusion

Our data suggest that the diastolic left ventricle does not behave as a simple unconstrained elastic shell (fig. 7). External forces, including pleural pressure, right ventricular pressure, and the pericardium, must be considered when interpreting measurements of left ventricular pressures and volumes, both at rest and during interventions. Geometric factors strongly determine how nonlinear elasticity of muscle relates to the ventricle's pressure-volume relationship. The fact that the theoretical equation, which accounts for the ventricle's wall thickness and chamber size, as well as the muscle's nonlinear elasticity, correlates well with the observed data suggests that these are the major considerations (fig. 7, top panel). Moreover, diastole is a dynamic process, and there is evidence that viscoelastic properties of cardiac muscle, which are sensitive to the rate of volume change, influence the pressure-volume relationship, particularly during atrial systole (fig. 7, lower panel). The rate of volume change during diastole depends on venous return, the duration of diastole, and the force of atrial systole.

It is difficult to assess whether disease directly affects the mechanical properties of passive cardiac muscle. Fibrosis, either as an aneurysm or interdigitating with cardiac muscle of normal stiffness, may increase overall wall stiffness. Wall stiffness, itself, is difficult to measure because of the need to factor out all of the other variables (fig. 7, lower panel), which together determine ventricular pressures and volumes and which are the only parameters readily accessible for measurements. Chronic cardiac disease markedly affects ventricular geometry (chamber size, wall thickness), which makes it particularly difficult to assess the effects of disease on intrinsic myocardial properties. All these factors are determinants of the diastolic pressure-volume relationship of the intact ventricle (fig. 7). This relationship, along with the rate and duration of ventricular volume inflow, determine end-diastolic fiber length and its stress. Our data suggest that the end-diastolic pressure cannot be readily used as a substitute for end-diastolic fiber length because hemodynamic interventions affect one or more of these determinants of the diastolic pressure-volume relationship in the intact ventricle. Moreover, shifts in diastolic pressure-volume curves during hemodynamic interventions invalidate attempts to quantitate ventricular stiffness using pressure and volume measurements made at analogous diastolic times, e.g., at end-diastole or pre-A wave.

In summary, frame-by-frame angiographic analysis in 16 patients showed that the theoretical equation (equation [2]), which defines the pressure-volume curve in terms of the nonlinear elasticity of the cardiac muscle itself correlated better with the observed diastolic pressure-volume curve in man than the commonly used empirical exponential equation (equation [1]). The interventions of nitroprusside and angiotensin markedly shifted the pressure-volume curve. The theoretical equation suggests that these shifts are not due to acute changes in the nonlinear elasticity of the myocardium itself, but rather to viscous effects, or more likely, to external mechanical loading on the left ventricle produced by changes in right ventricular pressure, and in the case of angiotensin, by restrictive action of the pericardium. The fact that the hemodynamic changes following these interventions did not, in general, simply move the left ventricle along a single diastolic pressure-volume curve indicates that one cannot derive end-diastolic circumferential fiber length from end-diastolic pressure alone. This result brings into serious question the practice of using end-diastolic pressure interchangeably with end-diastolic fiber length when interpreting experimental or clinical results in terms of the Frank-Starling mechanism.

Appendix

Cutting the sphere with a plane through its center reveals the forces in static equilibrium (fig. 8):

\[ \pi \sigma p = \pi \left[(r + h)p - r^3\right] \]

Divide both sides by \( \pi \sigma \) and let \( \eta = h/r; p = (2 + \eta) \sigma \)

Since the sphere is symmetric about all axes, it remains a sphere as it expands and the length of a muscle segment extending circumferentially around the sphere is \( x = (2\pi a)/2 = \pi (r + h)/2 \) \( \sigma a^2 + \pi \eta/2 \).

Substitute from \( a(x) = a [e^{(x^2)} - 1] \) (see Methods: Theoretical considerations) in order to obtain

\[ p = c \sigma (2 + \eta) [\rho/2 (x) - x] - 1 \]

Finally, use the equation for the volume of a sphere, \( V = (4/3)\pi r^3 \) to eliminate \( r \) from the last equation to obtain equation [2]. The rest length, \( x^* \), is half the sphere's circumference when \( p = 0 \).

References

2. Spottisowl HM, Sonesenbliek EH: Structural conditions in the hypertrophied and failing heart. Am J Cardiol 32: 393, 1973
Response to Exercise in Patients after Total Surgical Correction of Tetralogy of Fallot

FREDERICK W. JAMES, M.D., SAMUEL KAPLAN, M.D., DAVID C. SCHWARTZ, M.D.,
TE-CHUAN CHOU, M.D., MARY JO SANDKER, E.T., AND VERA NAYLOR, E.T.

SUMMARY Heart rate, blood pressure, physical working capacity, and electrocardiographic changes were evaluated during upright bicycle exercise in 43 asymptomatic patients, aged seven to 41 years, one to 14 years after total surgical correction of tetralogy of Fallot (TF). One hundred and nine normal subjects between the ages of five and 42 years served as controls.

The patient and control groups, subdivided by sex and body surface area (BSA), were similar in height and weight. When comparing males to males and females to BSA \( \geq 1.2 \text{ m}^2 \), maximal heart rates and working capacities were lower in the patient groups than in the control groups. An inverse relationship was observed between maximal working capacity and age at surgery in both male and female patient groups. By contrast, especially in the males with BSA < 1.2 \( \text{m}^2 \), the mean maximal heart rates and working capacities did not differ significantly between the patient and control groups.

Premature atrial or ventricular contractions were recorded in ten of 43 patients (23%) after exercise. Five of these ten patients had multifocal premature ventricular contractions (PVC) and four had unifocal PVC. In the five patients with multifocal PVC, a short burst of ventricular tachycardia occurred in two, coupling in one, and bigeminal rhythm in two. Cardiac arrhythmia was not observed in the control group. Although our current surgical results are excellent, this study suggests that impaired cardiovascular function persists after corrective surgery and that early surgical treatment may be more desirable. Furthermore, additional data suggest that the exercise procedure may be useful in detecting and managing patients who may develop life-threatening arrhythmias following intraventricular surgery.

ADEQUATE RELIEF OF RIGHT VENTRICULAR OUTFLOW TRACT (RVOT) obstruction without the development of significant pulmonary incompetence and closure of the ventricular septal defect are major goals for successful surgical treatment of tetralogy of Fallot. After intracardiac repair, symptoms of hypoxemia and severe exercise intolerance are relieved even in the presence of residual RVOT obstruction, pulmonary valve incompetence, and/or cardiomegaly.1 Despite dramatic symptomatic improvement after surgery for TF, cardiovascular performance at rest2 or during exercise3-10 may remain below normal, and major complications such as trifascicular block,11 complete heart block12,13 and sudden death14,15 may occur many years after surgical treatment.

Since ventricular arrhythmia and abnormal cardiovascular responses may occur as a result of physical stress, this study was designed to evaluate noninvasively the heart rate, blood pressure, physical working capacity, and electrocardiogram during strenuous upright bicycle exercise in patients who have had surgical repair of TF. The utility of noninvasive exercise testing in the management of patients who have had intraventricular surgery for congenital heart disease is discussed.

1. From the Department of Pediatrics (Cardiology), College of Medicine, University of Cincinnati, Children’s Hospital Medical Center, Cincinnati, Ohio.
2. Supported in part by the American Heart Association, Southwestern Ohio Chapter.
3. Address for reprints: Frederick W. James, M.D., Children’s Hospital Medical Center, Department of Pediatrics, Division of Cardiology, Cincinnati, Ohio 45229.
4. Received December 5, 1975; revision accepted May 13, 1976.
Acute hemodynamic interventions shift the diastolic pressure-volume curve in man.

E L Alderman and S A Glantz

*Circulation.* 1976;54:662-671
doi: 10.1161/01.CIR.54.4.662

*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1976 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/54/4/662

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Circulation* is online at:
http://circ.ahajournals.org//subscriptions/