PATHOPHYSIOLOGY AND NATURAL HISTORY

VALVULAR HEART DISEASE

Influence of aortic valve disease on systolic stiffness of the human left ventricular myocardium

THOMAS WISENBAUGH, M.D., JONATHAN L. ELION, M.D., AND STEVEN E. NISSEN, M.D.

ABSTRACT The new concept of systolic myocardial stiffness was applied to the study of ejection mechanics in aortic valve disease. Frame-by-frame analysis of stress (σ) and volume (V) was performed for two differently loaded beats in 26 patients who underwent simultaneous cineangiography and micromanometry; nine normal subjects, eight with isolated aortic regurgitation (AR), and nine with aortic stenosis (AS). Maximum myocardial stiffness (maxEm) was defined as the slope of the end-systolic (es) stress-strain relationship. End-systole was defined as the frame where stiffness was maximal, and strain was defined as ε = loge(Dm/Don), where Dm is left ventricular midwall diameter and Don is the theoretical Dm at zero stress. Expressed in terms of cavity volume, ε = γ · loge(V/Vo), where γ is the geometric factor relating Dm to V during systole. Vo was obtained by extrapolating to σes = 0 the function, σes = maxEm · γ · loge(Ves/Vo), which was fit to the end-systolic data. Vo always had a value greater than zero. MaxEm was preserved in the AR group (1575 ± 565) and increased in the AS group (1877 ± 544; p = .02) compared with normal (1320 ± 268), suggesting maintenance of contractile force per unit of myocardium in these two lesions. However, theoretical “unloaded” shortening fraction (SFu) was depressed in the AS group (0.30 ± 0.06; p = .01) compared with normal (0.37 ± 0.04), preserved in the AR group (0.34 ± 0.07; p = .24), and inversely related to maxEm (r = -.66, p = .01), suggesting a disparity between shortening potential and force potential. Systolic σ-V profiles had a characteristic pattern in the presence of AS when ejection fraction was normal, with stiffness approaching maximum earlier in ejection than in normal subjects or in the AR group. This difference in early systolic myocardial stiffness might be caused by ventricular resistance arising from different velocity profiles or from different aortic outflow resistance.


THE INOTROPIC STATE of hypertrophied human left ventricles has been assessed by various methods with differing results. Although the nature of the hypertrophy and the inciting stimulus may be important,1 methodologic differences may account for some of the disparities, since most of the methods previously used are limited by their load dependence.

The inotropic state of normal canine left ventricles has been assessed by the systolic elastance model.2 According to this model, active stiffening of the ventricular chamber during systole reflects, in part, the time course of myofilament activation2 and can be expressed as E(t) = P(t)/[V(t)-Vo], where E(t), P(t), and V(t) are the instantaneous values of chamber elasticity, pressure, and volume, respectively. Vo is the theoretical volume at zero total pressure (active plus passive) and can be derived from linear regression of P (tmax) against V (tmax) for differently loaded beats, where tmax is the time of maximal elastance near end ejection.3 Although the instantaneous pressure-volume relationship may be influenced by the extent and velocity of ejection4 and by the aortic input impedance,5 the Emax of the ventricle at end-systole is determined largely by inotropic state and not by circumstances earlier in the beat such as end-diastolic volume or the dynamics of the afterload.5,6

Although Emx is sensitive to short-term changes in inotropic state and relatively insensitive to short-term changes in load, its sensitivity to size7 confounds any comparison of function between normal and hypertrophied ventricles. It has therefore been suggested that stress-strain analysis is preferable to pressure-volume analysis for comparing stiffness between ventricles of different size, since stress effectively normalizes for
the influence of wall thickness on pressure, and strain normalizes for differences in volume.8

The primary goal of this study was to examine myocardial function in aortic valve disease using the new concept of systolic myocardial stiffness as derived from stress-strain analysis. A secondary objective was to examine the influence of aortic valve disease on the dynamics of systolic myocardial stiffness by analyzing stress-strain data frame by frame throughout systole.

Methods

Subjects. Three groups of patients were selected for study from among patients undergoing diagnostic cardiac catheterization at the University of Kentucky and the Lexington Veterans Administration Medical Centers from March 1985 to May 1986. The normal group comprised nine “normal” subjects who were catheterized to evaluate chest pain syndromes that were not typical of angina and who were found to have (1) normal coronary arteries, (2) a left ventricular ejection fraction of 0.55 or greater, (3) left ventricular angiographic wall thickness less than 1.1 cm, and (4) no evidence of valvular or hypertensive heart disease.

The AR group comprised eight patients with isolated aortic regurgitation graded on aortic root cine as 3 + to 4 + in severity (where 1 + indicates a trace of dye that is cleared from the ventricle with each systole, 2 + indicates faint opacification of the chamber, 3 + indicates dense opacification of the chamber comparable to that of the aorta after the third beat, and 4 + indicates that the root and chamber become equally opacified within 3 beats) with no more than a 15 mm Hg gradient between the peak left ventricular and peak aortic pressure. The AS group comprised nine patients with fixed aortic valvular (seven patients) or discrete subvalvular (two patients) stenosis with no more than 2 + aortic regurgitation.

Obstructive coronary artery disease was absent in all patients, all patients were in sinus rhythm, and the QRS duration did not exceed 0.11 sec. Clinical and hemodynamic data are shown in table 1. Each patient gave informed consent to a protocol approved by the joint University of Kentucky/VA Institutional Review Board.

Procedure. Patients were premedicated with 5 to 10 mg po diazepam. Long-term cardiac medications were not withheld for cardiac catheterization. Right heart catheterization was performed in all patients in the AR and AS groups. Left heart catheterization was performed retrogradely via the femoral or brachial artery with a No. 8F micromanometer catheter with a pigtail configuration. Left ventricular pressure was recorded simultaneously with injection of 39 to 54 ml of meglumine diatrizoate into the left ventricle during a cine angiography (30 degree right anterior oblique and 60 degree left anterior oblique). This was performed twice: once with and once without pharmacologic afterload manipulation. In all patients in the AR and AS groups, load was reduced by infusing sodium nitroprusside beginning at 0.25 μg/kg/min and increasing the dose by 0.25 μg/kg/min every 3 min to decrease aortic systolic pressure by 20% to 40% but to no less than 85 mm Hg. In the normal group, load was altered by one of three methods: ergonovine 0.35 mg iv in three divided doses in two patients, nitroglycerin 0.8 mg in two equally divided sublingual doses in three patients, or intravenous nitroprusside by the method described for the other groups. A 15 to 20 min interval separated the first and second ventriculograms to allow the hemodynamic effects of the contrast agent to dissipate. During this time neither the patient nor the imaging equipment were moved. Patients were instructed not to perform a Valsalva maneuver during inspiration held for the ventriculogram. Immediately after the second contrast cineangiogram, a radiographic grid positioned at mid chest was imaged in biplane fashion to provide corrections for magnification.

During the early period of study, the baseline cineangiogram was obtained before infusion of nitroprusside and the second angiogram. However, we soon learned that it was easier to reduce load with nitroprusside before rather than after the first injection of contrast. Subsequently, the nitroprusside angiogram was obtained first; the drug was then discontinued and the second angiogram obtained at 15 to 20 min later. This allowed for a greater difference in load between the two angiograms since the volume-loading effect of contrast further elevated pressures above baseline.

In one patient with aortic regurgitation, a third differently loaded beat was obtained for analysis by recording left ventricular pressure with a No. 5F micromanometer catheter positioned in the left ventricle while contrast was injected into the aortic root through the No. 8F pigtail micromanometer catheter.

Precise synchronization between pressure and cine was achieved with a cine frame marker, which records a mark for each film exposure (60/sec) simultaneously with the pressure recording and exposes every hundredth frame by means of a diode simultaneously with an accentuated mark on the pressure recording.

No patient experienced any symptom other than mild facial flushing during the infusion of nitroprusside, and there were no complications.

Analysis of catheterization data. Methods were similar to those used previously in this laboratory. Briefly, left ventricular silhouettes for each frame of the first well-opacified sinus beat of each left ventricular cine not preceded by a premature beat were digitized with a hand-held cursor. Left ventricular wall thickness was measured at the mid third of the anterior wall in the right anterior oblique view for the end-diastolic frame. Correction factors for ventricular measurements were derived from the grids positioned at the center of the ventricle. Left ventricular volume was computed by the area-length method and a regression equation. Since the silhouette borders in the left anterior oblique view were sometimes unclear over the spine and diaphragm, and since segmental dysynchrony was absent, volumes were computed from the single-plane right oblique view. Left ventricular mass was computed from wall thickness measured at end-diastole. Dynamic wall thickness was computed for all frames subsequent to end-diastole assuming a constant mass for each frame, according to the method of Hugenholtz et al.12 Left ventricular pressure for the corresponding cardiac cycle was digitized with the mid portion of the QRS complex used as a reference point for end-diastole.

As suggested by Mirsky and associates,8,11 the stress difference (σ) was used to compute systolic myocardial stiffness, i.e., the difference between the circumferential (σθ) and radial (σr) stress components averaged across the entire wall thickness: σ = σθ - σr, where σθ = 1.332 - (PD/m)2h; 1 - h/Dm = Dm2 + 2Lm2, Lm = -1.332 - (PD/m)2h; P is pressure, h is wall thickness, and Dm and Lm are diameter and length, respectively, at the midwall.

Strain was defined as ε = log (Dm/Dm0), where Dm0 is the theoretical Dm at zero stress. Midwall rather than endocardial dimensions were used for the analysis of strain, since the endocardial shortening is significantly influenced by the D: h ratio.14 In terms of cavity volume, strain can be defined alternatively as ε = γ · log (V/V0), where V0 is the zero stress volume and γ is the geometric factor relating systolic Dm to V in the equation Dm = A · Vγ, where A is a regression constant. V0 and maxE0 are obtained by fitting the end-systolic data, which were
not smoothed, to the relationship: \( \sigma_{E_s} = \max E_{av} \cdot \gamma \cdot \log \left( \frac{V_{o}}{V_{d}} \right) \), where \( \max E_{av} \) (maximum myocardial stiffness based on the average stress difference) is the slope and \( V_{o} \) is the intercept.

For this analysis, an initial value of \( V_o \) was approximated by the appropriate extrapolation; the maximum slope of the \( \sigma-\varepsilon \) relationship was obtained by a modification of the method of Kono et al. Briefly, this is an iteration that first finds the maximum quotient of \( \sigma(t)/\varepsilon(t) \) for each loop, then performs a three-point linear regression using these two values with the first approximation of \( V_o \) as the third point. A second approximation of \( V_o \) is obtained from this regression equation, and the process is repeated until convergence occurs on a maximum value for the slope with a final value for \( V_o \).

To detect disparities between chamber stiffening potential (i.e., \( \max E_{av} \)) and shortening potential, which have been observed in other studies, the theoretical "unloaded" ejection fraction was computed from the diastolic volume at a common preload and systolic volume at zero stress: \( \frac{E_{f}}{V_{d}} = \frac{(V_{d} - V_{o})}{V_{d}} \), where \( V_{d} \) is the diastolic volume at a common preload, \( E_{f} = 60 \text{ kdyn/cm}^2 \). A three-constant exponential equation was fit to the diastolic stress-volume data, \( E_{f} = a + b \cdot e^{c \cdot V_{d}} \), and solved for \( V_{d} \) at \( E_{f} = 60 \). Since ejection performance based on endocardial motion is not uniquely dependent on fiber shortening, but also on the \( D/h \) ratio, unloaded fiber shortening was also estimated as \( S_{F_{o}} = \frac{(D_{dm} - D_{om})}{D_{alm}} \), where \( D_{dm} \) is midwall diameter at \( \sigma_{E} = 60 \text{ kdyn/cm}^2 \). The volume-time data from late diastole of one beat through early diastole of the next beat was fit to an eleventh-order polynomial equation. This function allowed for computation of instantaneous ejection velocity at any time during systole by taking the first derivative of the function with respect to time. A polynomial of eleventh order was found to give sufficient smoothing of the data but did not severely dampen important events such as the atrial kick.

Group comparisons were performed by analysis of variance with a post hoc multiple comparison test (SYSTAT, Inc.), using the Bonferroni method to adjust the overall error rate of .05 for multiple comparisons (e.g., critical level = \( \alpha/k \cdot 0.05 = 0.05/2 = 0.025 \), where \( k \) is the number of comparisons).

**Results**

Clinical and catheterization data for each patient are listed in table 1. The influence of pharmacologic load manipulation on the angiographic and hemodynamic variables is presented in table 2.

Left ventricular chamber volumes were significantly increased above normal in the AR group but not in the

---

**Table 1**

Clinical and catheterization data

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>BSA (m²)</th>
<th>FC</th>
<th>AVG (mm Hg)</th>
<th>AR</th>
<th>Etiology</th>
<th>Cardiac Meds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>61</td>
<td>1.85</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Nifed, ntg</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
<td>2.04</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>55</td>
<td>2.01</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Dig, Diur</td>
</tr>
<tr>
<td>4</td>
<td>34</td>
<td>1.86</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Diur</td>
</tr>
<tr>
<td>5</td>
<td>42</td>
<td>1.92</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Beta, ntg</td>
</tr>
<tr>
<td>6</td>
<td>59</td>
<td>1.86</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Nifed, ntg</td>
</tr>
<tr>
<td>7</td>
<td>47</td>
<td>2.02</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Beta, ntg</td>
</tr>
<tr>
<td>8</td>
<td>41</td>
<td>2.21</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Ntg</td>
</tr>
<tr>
<td>9</td>
<td>53</td>
<td>1.93</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Beta</td>
</tr>
<tr>
<td>AR group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>61</td>
<td>1.96</td>
<td>IV</td>
<td>0</td>
<td>4+</td>
<td>Unknown</td>
<td>Dig, diur</td>
</tr>
<tr>
<td>11</td>
<td>66</td>
<td>1.90</td>
<td>II</td>
<td>0</td>
<td>3+</td>
<td>Unknown</td>
<td>Diur</td>
</tr>
<tr>
<td>12</td>
<td>53</td>
<td>1.52</td>
<td>IV</td>
<td>0</td>
<td>4+</td>
<td>Unknown</td>
<td>Beta, hydral, diur</td>
</tr>
<tr>
<td>13</td>
<td>33</td>
<td>1.62</td>
<td>II</td>
<td>7</td>
<td>3-4+</td>
<td>Rheumatic</td>
<td>None</td>
</tr>
<tr>
<td>14</td>
<td>68</td>
<td>1.70</td>
<td>IV</td>
<td>0</td>
<td>3+</td>
<td>Unknown</td>
<td>Dig, diur, hydral</td>
</tr>
<tr>
<td>15</td>
<td>45</td>
<td>1.98</td>
<td>III</td>
<td>0</td>
<td>4+</td>
<td>Unknown</td>
<td>Prazosin</td>
</tr>
<tr>
<td>16</td>
<td>68</td>
<td>2.01</td>
<td>II</td>
<td>0</td>
<td>3-4+</td>
<td>Floppy</td>
<td>Diur</td>
</tr>
<tr>
<td>17</td>
<td>22</td>
<td>1.91</td>
<td>II</td>
<td>0</td>
<td>3+</td>
<td>Congenital</td>
<td>None</td>
</tr>
<tr>
<td>AS group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>63</td>
<td>2.02</td>
<td>III</td>
<td>68</td>
<td>—</td>
<td>Calcific</td>
<td>Quin</td>
</tr>
<tr>
<td>19</td>
<td>20</td>
<td>1.56</td>
<td>II</td>
<td>60</td>
<td>2+</td>
<td>Subvalvular</td>
<td>None</td>
</tr>
<tr>
<td>20</td>
<td>70</td>
<td>1.72</td>
<td>III</td>
<td>55</td>
<td>—</td>
<td>Calcific</td>
<td>Diur</td>
</tr>
<tr>
<td>21</td>
<td>19</td>
<td>1.59</td>
<td>II</td>
<td>70</td>
<td>1-2+</td>
<td>Subvalvular</td>
<td>None</td>
</tr>
<tr>
<td>22</td>
<td>65</td>
<td>1.94</td>
<td>IV</td>
<td>65</td>
<td>—</td>
<td>Calcific</td>
<td>Dobut, Procan, diur</td>
</tr>
<tr>
<td>23</td>
<td>63</td>
<td>1.85</td>
<td>III</td>
<td>100</td>
<td>—</td>
<td>Calcific</td>
<td>None</td>
</tr>
<tr>
<td>24</td>
<td>56</td>
<td>1.98</td>
<td>III</td>
<td>45</td>
<td>0</td>
<td>Calcific</td>
<td>None</td>
</tr>
<tr>
<td>25</td>
<td>62</td>
<td>2.02</td>
<td>III</td>
<td>82</td>
<td>—</td>
<td>Calcific</td>
<td>None</td>
</tr>
<tr>
<td>26</td>
<td>68</td>
<td>1.84</td>
<td>IV</td>
<td>80</td>
<td>—</td>
<td>Calcific</td>
<td>Dig, diur</td>
</tr>
</tbody>
</table>

BSA = body surface area; FC = NYHA functional class; AVG = peak-to-peak aortic valve gradient; AR = angiographic grade of aortic regurgitation; dig = digoxin; diur = diuretic; ntg = long-acting nitrate; hydral = hydralazine; procan = procainamide; nifed = nifedipine; beta = beta blocker; dobut = dobutamine at 7.5 \( \mu g/kg/min \) iv.
TABLE 2
Angiographic and hemodynamic data (mean ± SD)

<table>
<thead>
<tr>
<th></th>
<th>EDVI (ml/m²)</th>
<th>ESVI (ml/m²)</th>
<th>EF (%)</th>
<th>LVESP (mm Hg)</th>
<th>σ₀ (kdyne/cm²)</th>
<th>σ₁ (kdyne/cm²)</th>
<th>HR (beats/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>81 ± 16</td>
<td>28 ± 7</td>
<td>0.65 ± 0.05</td>
<td>126 ± 15</td>
<td>274 ± 54</td>
<td>63 ± 28</td>
<td>66 ± 12</td>
</tr>
<tr>
<td>AR</td>
<td>75 ± 12</td>
<td>24 ± 6</td>
<td>0.68 ± 0.05</td>
<td>113 ± 27</td>
<td>217 ± 105</td>
<td>44 ± 35</td>
<td>70 ± 13</td>
</tr>
<tr>
<td>AR</td>
<td>186 ± 15B</td>
<td>93 ± 52B</td>
<td>0.53 ± 0.14</td>
<td>149 ± 28</td>
<td>375 ± 38</td>
<td>120 ± 46B</td>
<td>70 ± 8</td>
</tr>
<tr>
<td>AR</td>
<td>160 ± 57B</td>
<td>67 ± 44B</td>
<td>0.61 ± 0.12</td>
<td>119 ± 21</td>
<td>224 ± 51</td>
<td>64 ± 39</td>
<td>72 ± 8</td>
</tr>
<tr>
<td>AS</td>
<td>102 ± 19</td>
<td>45 ± 24</td>
<td>0.57 ± 0.17</td>
<td>203 ± 25B</td>
<td>365 ± 136</td>
<td>93 ± 39</td>
<td>76 ± 8</td>
</tr>
<tr>
<td>AS</td>
<td>91 ± 19</td>
<td>37 ± 25</td>
<td>0.60 ± 0.21</td>
<td>185 ± 20B</td>
<td>287 ± 133</td>
<td>51 ± 44</td>
<td>82 ± 12</td>
</tr>
</tbody>
</table>

Data were obtained during pharmacologic load intervention (2) and during basal conditions (1).

EDVI = end-diastolic volume index; ESVI = end-systolic volume index; EF = ejection fraction; LVESP = left ventricular peak systolic pressure; HR = heart rate.

aMean values include two patients (1 and 2) in whom load was augmented with ergonovine; in all others, vasodilating drugs were used.

AS group (table 2). Left ventricular mass was significantly (p < .005) increased in the AS (173 ± 32 g/m²) and AR groups (214 ± 77 g/m²) compared with that in the normal group (96 ± 15 g/m²). Ejection fraction varied widely within the AR and AS groups and was not significantly depressed for either group (table 2).

Decreases in left ventricular peak systolic pressure and end-systolic stress produced by pharmacologic vasodilation were associated with minor increases in heart rate of 6% for the normal group, 3% for the AR group, and 8% for the AS group (table 2).

The frame-by-frame stress-volume data for two patients from each group and the function fit to the end-systolic data are presented in figure 1. The extent to which volume and stress could be altered by the vasodilating drugs is illustrated in this figure.

The maxEav and V₀ data obtained from the nonlinear σ₀-V₀ relations for each group are presented in table 3. Systolic myocardial stiffness measured as maxEav was well preserved in both abnormal groups, with a trend toward higher values than normal that was significant in the AS group (p = .02 for AS vs normal). In no patient in either the AS or AR group did maxEav fall below the normal range of values. There was no significant relationship between ejection fraction and systolic myocardial stiffness (figure 2). Values of V₀ were positive in all patients.

In view of the seeming paradox of increased normalized systolic chamber stiffness in the presence of myocardial damage noted by others,7,17 additional indexes of performance derived from stress-volume relations were examined, namely theoretical ejection fraction (EF₀) and shortening fraction (SF₀) from a common preload to zero afterload (table 3). Unloaded shortening at the midwall (SF₀) was significantly less than normal in the AS group (p = .01) but not in the AR group (p = .24 vs normal). EF₀ was slightly reduced in both abnormal groups, but the differences were not statistically significant (p = .08 for AS vs normal and p = .07 for AR vs NL). For the AS and AR groups combined, EF₀ (0.80 ± 0.09) was significantly (p = .04) less than normal (0.87 ± 0.03). There were significant (p < .01) inverse correlations between maxEav and EF₀ (figure 3) and between maxEav and SF₀ (r = −.66).

The shapes of the stress-volume loops as represented in figure 1 suggested that aortic outflow obstruction may influence the time course of myocardial stiffness. In the presence of aortic obstruction, peak stress for the more afterloaded beats more nearly approached the maximum stress defined by the maximum stiffness relation than it did in either normals or patients with aortic regurgitation, with ejection occurring along the line of maximum stiffness in late systole. Since it is known that the velocity of shortening may influence

TABLE 3
Data derived from stress (σ)-strain (ε) analysis (mean ± SD)

<table>
<thead>
<tr>
<th></th>
<th>maxEav (kdyne/cm²)</th>
<th>V₀ (ml/m²)</th>
<th>EF₀ (%)</th>
<th>SF₀ (%)</th>
<th>HR (beats/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>1320 ± 268</td>
<td>22 ± 6</td>
<td>0.87 ± 0.03</td>
<td>0.37 ± 0.04</td>
<td></td>
</tr>
<tr>
<td>AR</td>
<td>1575 ± 565</td>
<td>68 ± 57A</td>
<td>0.80 ± 0.09</td>
<td>0.34 ± 0.07</td>
<td></td>
</tr>
<tr>
<td>AS</td>
<td>1877 ± 544A</td>
<td>35 ± 20</td>
<td>0.80 ± 0.09</td>
<td>0.30 ± 0.06A</td>
<td></td>
</tr>
</tbody>
</table>

maxEav = maximum myocardial stiffness; V₀ = volume extrapolated to zero stress; EF₀ = theoretical unloaded ejection fraction; SF₀ = theoretical unloaded shortening fraction.

aSignificant difference from normal in AR and AS.
FIGURE 1. For legend see opposite page.
instantaneous pressure-volume relationships, a comparison of ejection rate among groups was performed. There were no significant differences in mean normalized systolic ejection rate among groups (normal, 2.49 ± 0.45; AR, 2.26 ± 0.51; AS, 2.35 ± 0.34 for “unloaded” beats [p = NS] and normal 1.91 ± 0.39; AR, 1.65 ± .33; AS, 1.77 ± 0.25 for “loaded” beats [p = NS]). However, there were characteristic differences in the velocity profiles between the normal and AS groups as illustrated in figure 4, with peak velocity occurring relatively early in systole for normals, compared with a broad, flat velocity profile or even late peaking velocity in patients with AS.

Discussion

Force potential measured as maxEav was well preserved in both groups with aortic valve disease. However, shortening potential measured as SFo was depressed in patients with aortic stenosis and was inversely related to force potential. The basis for using these indexes of function, and the relevance of these results to previous studies, will be discussed.

The use of the end-systolic pressure-volume relationship (ESPVR) to assess short-term changes in ventricular contractile function has a basis in muscle mechanics. In excised papillary muscle, stimulated to contract in either the isometric or isotonic mode, an inotropic stimulus produces an increase in the slope of the relationship between total force and length. The ESPVR is analogous to the force-length relationship; its slope, termed Emax by Suga and Sagawa, is also sensitive to short-term inotropic interventions, but it may be somewhat affected by several other factors such as shortening deactivation and arterial impedance. An important factor that confounds the comparison of inotropic state between ventricles of different size with the ESPVR is that it is dependent on the size of the chamber and thickness of the wall. To normalize for the size-dependence of the ESPVR, Mirsky et al. have proposed that the analysis of stress and strain be used to compute systolic myocardial stiffness, maxEav (as opposed to systolic chamber stiffness or Emax). The stress-strain relationship for the ventricle should be directly related to the relationship between force and normalized length for isolated muscle, and this relationship describes the total systolic force that can be attained at any given degree of stretch.

The velocity-force relationship describes the velocity of muscle shortening at any given load. A depression in both the velocity-load and shortening-load relationship have been observed in experimental models of pressure overload. By the latter relationship, shortening deficits have identified patients with either aortic stenosis or aortic insufficiency. However, the ejection fraction–afterload relationship is limited as a measure of inotropic state by the extent to which ejection fraction is dependent on resting length (“preload”).

FIGURE 2. Ejection fraction (EF) was not significantly related to maximum myocardial stiffness (maxEav). NL = normal.

FIGURE 3. A significant (p < .01) inverse relationship was found between the theoretical unloaded ejection fraction (EFo, obtained from the volume at zero systolic stress and volume at a common diastolic stress) and maxEav. NL = normal.
this study, ejection (EF) and midwall shortening (SF) to zero load from a common preload were used to estimate shortening potential (the latter is preferable to EF, in that it is independent of the diameter:thickness ratio). This was a means of adjusting for differences between patients in preload as well as afterload.

The contractile state of human myocardium hypertrophied by pressure overload has been a subject of controversy for several years. Fifer et al. found that the rate of force development (dF/dt) was preserved in a group of patients with severe aortic stenosis, even in several in whom the ejection fraction was depressed (0.33 to 0.44). The finding that depressed ejection performance was accompanied by elevated systolic stress led Gunther and Grossman to conclude that afterload mismatch, and not contractile impairment, was responsible for depressed performance. However, Huber et al. derived subnormal values of maximum shortening velocity (Vmax) in subsets of patients with aortic stenosis in whom hypertrophy was severe. This result was corroborated by Wisenbaugh et al. with ejection fraction–afterload relationships indicating that shortening deficits could not be attributed solely to afterload mismatch. In this study, shortening potential measured as SFe was inversely related to force potential measured as maxEa and tended to be depressed in patients with aortic valve disease (although SFe was significantly depressed only in the AS group). Thus one could speculate that differences in results among previous studies of aortic stenosis lie in the different methods of estimating contractile state: those based on force, which demonstrated normal function, and those based on shortening potential, which demonstrated abnormal function.

There is precedent for the concept that some pathologic processes may produce a disparity between systolic stiffness and shortening potential. Sunagawa et al. and Little et al. found that regional ischemia, which impairs pumping performance of the ventricle, produced a parallel rightward shift in the ESPVR, which amounts to an increase in V normalized chamber stiffness. Likewise, when Suga et al. reanalyzed ESPVR data previously published by others, increased normalized chamber stiffness was found in patients with decompensated congestive heart failure. In a study of stress-diameter relations in the porcine hypertrophied left ventricle after a long-term pressure overload, increased diameter intercepts with normal stress-diameter slopes were observed, indicating increased myocardial stiffness; in contrast, theoretical “unloaded” shortening (based on the relation between end-systole diameter at zero systolic stress and diameter at end-diastole) was depressed in those animals with the most extensive hypertrophy. Bulk series elastic stiffness might explain increased normalized systolic chamber stiffness with regional ischemia. An alternative explanation for these apparent disparities between systolic stiffness and shortening is that increased stiffness results in increased resistance to shortening. It should also be noted that systolic stiffness is not a purely active stiffness since it is based on total stress and therefore involves both active and passive effects of volume changes.

Mirskey et al. has recently modeled stress-volume relations according to the concept that the ventricle becomes so stiff during contraction that it behaves like a Hookean material with a constant modulus of stiffness during late systole. The constant stiffness during mid-to-late systole observed in patients with severe aortic stenosis in whom ejection fraction was preserved is consistent with this concept. However, systolic stress did not approach that defined by the maximum stiffness relation until near end-ejection in the normal or AR groups. The apparent difference in dynamic stiffness between AS versus normal and AR might be the result of (1) greater pressure deficits in early compared with late systole in the absence of aortic stenosis because of the more rapid velocity of shortening in early systole, i.e., the effects of internal resistance described by Hunter et al., or (2) resistance at the valvular level in aortic stenosis, which might allow the ventricle to “stiffen” earlier in systole than normal, i.e., greater isometric tension development before ejection occurs.

Mirskey’s maximum stiffness model predicts that systolic stress-diameter strain relations will be linear
and, since volume and diameter do not share a linear relationship, pressure-volume relations will be nonlinear. This model differs from the maximal elastance model of Suga et al.7 and Sagawa,8 which predicts linear pressure-volume relations. Which model more accurately predicts stress-volume relations in humans with normal and, more importantly, dilated ventricles cannot be ascertained from our results, since only two differently loaded beats were analyzed in all but one patient.

The use of only two differently loaded beats represents a significant limitation of our study. However, we do not feel it is safe to perform more than two ventriculograms in patients with impaired hemodynamics using the amount of contrast that is currently used. This means that autonomic blockade is not considered unsafe to use in myocardial mechanics using the amount of contrast that is currently used. Thus it is probable that small changes in myocardial contractility occurred in response to load alteration between the two ventriculograms, as indicated by the small changes in heart rate that were observed (see table 2). Also, we cannot be certain that the three different drugs used to alter load within the normal group produce equivalent stress-strain data. Finally, it should be noted that maxEw, SFw, and EFo are each subject to errors of extrapolation because they depend on V0.

In summary, it appears that alterations in the end-systolic stress-volume relationship associated with chronic hypertrophy are more complex (due to concomitant increases in V0) than alterations produced by short-term inotropic interventions. Although the finding of normal or increased maxEw is consistent with the concept that hypertrophy is an adaptation to hemodynamic loading in which contractile force per unit of myocardium is maintained,1 shortening ability measured by EFSV relations9,20 or SFw may be depressed in patients with aortic stenosis and aortic regurgitation. Whether maxEw is less sensitive to long-term changes in contractility than are shortening indexes, or whether it actually measures a different facet of contractility, is unclear at this time.

We thank Donna Wisenbaugh for proof reading the manuscript and Charles Fischer for expert assistance with the laser graphics.

Appendix

Equations for left ventricular volume, mass, and dynamic wall thickness10–12:

1. V = 0.938 [0.849 · Athrρ2]/Lthr — 5.7 ml

where V = volume, Atrρ = area in RAO projection (corrected), and Lthr = length in RAO projection (corrected).

2. LVM = [(π/6) · (L + 2h) · (D + 2h)2 · EDV] · 1.05

where LVM = left ventricular wall mass, L = ventricular cavity length, D = ventricular cavity diameter, h = wall thickness, and EDV = end-diastolic cavity volume.

Iteration of three equations:

3. g(h) = h3 + h2 · (L/2 + D) + h · (L/2 + D/2) + 3 · LVM/4π/1.05

4. g'(h) = 3h2 + h · (L + 2D) + L/2 + D/4

5. h = ln g(h)/g'(h)

is performed until convergence on the solution for dynamic wall thickness (h), where g(h) is a function of h and g'(h) is the first derivative of the function.

6. EF = SV/EDV

where SV = stroke volume and EDV = end diastolic cavity volume.

7. MNSER = EF/ET

where MNSER = mean normalized systolic ejection rate and ET = ejection time measured from onset to end-ejection.

References


23. Little WC, O'Rourke RA: Effect of regional ischemia on the left ventricular end-systolic pressure-volume relation in chronically instrumented dogs. J Am Coll Cardiol 5: 297, 1985
Influence of aortic valve disease on systolic stiffness of the human left ventricular myocardium.

T Wisenbaugh, J L Elion and S E Nissen

_Circulation_. 1987;75:964-972
doi: 10.1161/01.CIR.75.5.964

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1987 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/75/5/964

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/