The superiority of maximum fiber elastance over maximum stress-volume ratio as an index of contractile state

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ABSTRACT The end-systolic pressure-volume relationship has been used as a load-independent measure of ventricular pump performance. Since comparisons of load between ventricles of different size and thickness may be more accurately made with measurements of wall stress than with those of pressure, the end-systolic stress-volume relationship at one or more levels of end-systolic stress has been used to estimate contractile function in hypertrophied ventricles. Linear regression of end-systolic stress against end-systolic volume for differently loaded beats has a slope termed maximum fiber elastance (fiber Emax) and a volume intercept termed Vo; the maximum stress-volume ratio (MSVR) for a single beat is an approximation of fiber Emax but assumes Vo = 0. However, the influence of preload, afterload, and inotropic state on these indexes has not been examined. We therefore studied the stress-volume relationship in seven open-chest dogs instrumented with ultrasonic crystals and micromanometers. Postextrasystolic potentiation (PESP) increased both the MSVR (5.7 ± 1.83 vs 4.85 ± 1.43 at control, p < .05) and fiber Emax (13.93 ± 3.24 vs 9.24 ± 2.15 at control; p < .05). Augmentation of preload by infusion of dextran, with the use of nitroprusside to maintain afterload relatively constant, did not significantly influence either the MSVR or fiber Emax. Vo was not significantly influenced by PESP, but was shifted to higher values by augmentation of preload (17.5 ± 14.8 vs 13.9 ± 11.1 ml at control; p < .05). Augmentation of afterload by aortic constriction was used to derive fiber Emax, and produced an increase in MSVR directly proportional to the increase in wall stress (6.03 ± 1.39 with end-systolic stress augmented by 93% vs 4.85 ± 1.43 at control; p < .05). Thus, MSVR is a less reliable index of inotropic state than fiber Emax since it is afterload dependent.


THE END-SYSTOLIC pressure-volume relationship has been used as a preload-independent measure of ventricular pump performance.1,3 Since the load on myocardial fibers comprising the ventricle depends not only on intraventricular pressure, but also on wall thickness and chamber dimensions, it has been proposed that in hypertrophied ventricles stress is a better measure of load than is pressure.4,5 Several investigators have therefore used either the end-systolic stress-volume relationship for differently loaded beats6 or the end-systolic stress-volume ratio from a single beat7–9 to estimate contractile function in chronically overloaded ventricles. However, existing data are not sufficient to clearly define the sensitivity of either the stress-volume ratio or the slope of the stress-volume relationship at end-systole to changes in contractile state. We therefore examined the effects of postextrasystolic potentiation (PESP) of inotropic state and of altered ventricular volume and load on the maximum stress-volume ratio (MSVR) and the slope of the end-systolic stress-volume relationship (fiber Emax) in open-chest dogs instrumented with sonomicrometer crystals and micromanometer-tip pressure transducers.

Methods

Animal studies were conducted in accordance with the guidelines of the American Physiologic Society. Adult mongrel dogs anesthetized with 1 mg/kg im morphine, 350 mg/kg iv urethane, and 45 mg/kg iv α-chloralose were ventilated on a respirator through an endotracheal tube. Through a left lateral thoracotomy, the pericardium was opened and two orthogonal pairs of 5 MHz piezoelectrical crystals 5 mm in diameter were sutured at the major and minor axes, as previously described.6 A snare was placed around the descending thoracic aorta. Through branches of the femoral artery, No. 7F micromanometer-tip catheters were introduced into the left ventricle and proximal aorta. A large-bore cannula was inserted into the inferior vena cava through a femoral vein. Bipolar epicardial electrodes were su-
tured to both the left atrium and left ventricle. Autonomic blockade was produced with 0.1 mg/kg atropine and 2 mg/kg iv propanol; adequacy of β-blockade was assessed by determining the dose of isoproterenol required to produce a 25% increase in heart rate both before and after administration of propranol. Heart rate was maintained just above intrinsic rate (120 to 150 beats/min) by atrial pacing. Left ventricular dimensions were measured with a sono micrometer (Triton Industries) and recorded on a strip-chart recorder and on 16-channel magnetic tape simultaneously with aortic pressure, left ventricular pressure, left ventricular dP/dT, and the electrocardiogram. Measurements were made at four to five different levels of aortic pressure, each produced by tightening the snare during an 8 to 10 sec interruption of ventilation.

PESP was produced by premature ventricular stimuli delivered at a coupling interval of 200 msec by a programmable pacemaker (Medtronic) each eighth beat at each level of pressure. Myocardial length (or preload), measured as left ventricular end-diastolic dimensions, was increased by rapid infusion of 250 ml dextran. Intravenous nitroprusside was used to maintain constant aortic pressure. Measurements were again made at this and three to four higher levels of aortic pressure produced by tightening the aortic snare. Each experiment was terminated by inducing fibrillation of the heart, which was then removed. The left ventricle, including the septum, was weighed after it was separated from the right ventricle and atria. Data were digitized at 5 msec intervals and transferred to floppy disks with an analog-to-digital convertor (Data Acquisition Systems) and microcomputer (IBM PC). Beats just before and after the programmed premature stimulus at each level of varied loading were chosen for analysis.

Ventricular volume was calculated with the equation of Rankin et al. as follows:

\[ V_i = \left( \frac{\pi}{6} \right) (a - 1.1h)(b - 2h)^2 \]  (1)

where \( V_i \) is the dynamic internal volume of a prolate ellipsoidal shell in which \( b \) is the external diameter of the minor axis, \( a \) the external diameter of the major axis, and \( h \) is the equatorial wall thickness.

The external shell volume (\( V_e \)) was calculated from the equation

\[ V_e = \left( \frac{\pi}{6} \right) (ab)^2 \]  (2)

Since the myocardial volume (\( V_m = V_e - V_i \)) can be computed from the measured postmortem mass of the left ventricle and the specific gravity of the myocardium (1.06 g/cm³), wall thickness can be determined from simultaneous solution of equations 1 and 2. This is done by computer iteration with the Newton Raphson method. Briefly, iteration of the three following computations is performed until convergence on the solution for \( h \):

\[ g(h) = 1.1h^3 - (a + 1.1b)h^2 + (ab + 1.1b^4)/4 - 3V_m/2\pi \]  (3)
\[ g'(h) = 3.3h^2 - 2(a + 1.1b)h + (ab + 1.1b^4)/4 \]  (4)
\[ h = 1h - g(h)/g'(h) \]  (5)

where \( g(h) \) is a function of \( h \), \( g'(h) \) is the first derivative of the function, and \( 1h \) represents the value of \( h \) from the preceding iteration. This is the method used by Hugenholtz et al. for computing dynamic thickness from left ventriculograms in humans. Mean circumferential wall stress is then computed at 5 msec intervals throughout the cardiac cycle with Mirsky’s equation for a thick wall ellipse as follows:

\[ S = 1.33(Pb/2h)(1 - b^2/(2a^2) - h/b) \]  (6)

The end-systolic stress-volume relationship was derived from each series of stress-volume loops with the iterative method of Kono et al. that first locates the end-systolic stress-volume coordinate on each loop and then performs a linear regression on these points. Since we used stress rather than pressure as a measure of afterload in this study, we have referred to the slope of this relationship as fiber Emax to differentiate this quantity from chamber Emax, as used by Sagawa and his colleagues. The MSVR within each loop, which assumes an intercept of \( V_o = 0 \), was also determined by the computer, which then plotted each loop. Comparisons of MSVR for single beats were made under control conditions, both for a regular atrial and a potentiated beat, with afterload (end-systolic stress) augmented by approximately 100% of control, and with preload augmented while afterload was held constant.

**Statistical analysis.** Analysis of covariance was used to establish whether or not significant differences in the Emax were produced in each dog by PESP (SYSTAT, Inc.). Comparisons of values for fiber Emax and other parameters under different states were made by analysis of variance for repeated measures and the multiple-comparison test of Dunnett.

**Results**

The morphologic and baseline hemodynamic characteristics of the dogs are listed in table 1. The hemodynamic responses to PESP, volume loading, and pressure loading are shown in table 2.

Fiber Emax was significantly increased by PESP in each dog, with a mean increase of 51% for the group (p < .05). Fiber Emax was not significantly altered by augmentation of preload with infusion of dextran-nitroprusside. The volume intercept, \( V_o \), was not altered by inotropic stimulation with PESP, but was shifted to a larger value by dextran-nitroprusside. An example of the influence of PESP on fiber Emax and \( V_o \) is illustrated in figure 1, and the data are summarized in table 3.

**Table 1**

**Morphologic and hemodynamic data**

<table>
<thead>
<tr>
<th>Dog</th>
<th>Body weight (kg)</th>
<th>LV weight (g)</th>
<th>HR (bpm)</th>
<th>LVSP (mm Hg)</th>
<th>LVEDP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>437</td>
<td>22.5</td>
<td>107</td>
<td>150</td>
<td>106</td>
<td>7</td>
</tr>
<tr>
<td>344</td>
<td>22.4</td>
<td>82</td>
<td>160</td>
<td>108</td>
<td>5</td>
</tr>
<tr>
<td>438</td>
<td>17.5</td>
<td>64</td>
<td>150</td>
<td>103</td>
<td>6</td>
</tr>
<tr>
<td>567</td>
<td>20.5</td>
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<td>150</td>
<td>78</td>
<td>8</td>
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<tr>
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<td>103</td>
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<tr>
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<td>20.0</td>
<td>73</td>
<td>150</td>
<td>110</td>
<td>8</td>
</tr>
<tr>
<td>663</td>
<td>24.5</td>
<td>106</td>
<td>130</td>
<td>153</td>
<td>8</td>
</tr>
<tr>
<td>Mean</td>
<td>21.1 ± 2.2</td>
<td>90 ± 18</td>
<td>14 ± 14</td>
<td>± 24</td>
<td>± 1</td>
</tr>
</tbody>
</table>

Table 1

| LV = left ventricular; HR = heart rate; LVSP = LV systolic pressure; LVEDP = LV end-diastolic pressure. |
TABLE 2
Hemodynamic response to intervention (mean ± SD)

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>PESP</th>
<th>Volume loading</th>
<th>Pressure loading</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVSP</td>
<td>113 ± 24</td>
<td>135 ± 30(^{A})</td>
<td>113 ± 25</td>
<td>160 ± 38(^{A})</td>
</tr>
<tr>
<td>LVEDP</td>
<td>7 ± 1</td>
<td>9 ± 3</td>
<td>9 ± 2</td>
<td>10 ± 3</td>
</tr>
<tr>
<td>Maximum</td>
<td>1874 ± 560</td>
<td>3182 ± 909(^{A})</td>
<td>2396 ± 470(^{A})</td>
<td>2083 ± 458</td>
</tr>
</tbody>
</table>

Hemodynamic conditions listed in the pressure loading column are those under which MSVR volume ratio was analyzed. Abbreviations and units are as in table 1.

\(^{A}\)Significant (p < .05) difference from control by ANOVA.

PESP produced a modest but significant increase (19%) in the MSVR ratio for single beats under control conditions, as illustrated in figure 2, left. The relatively pure increase in preload produced by infusion of dextran-nitroprusside was sufficient to produce a 30% increase in mean end-diastolic volume, but did not significantly alter MSVR. This is illustrated in figure 2, center. However, a mean increase of 93% in end-systolic stress produced by aortic constriction resulted in a 24% increase in the MSVR, as illustrated in figure 2, right. Thus, the single-beat MSVR was sensitive to the inotropic stimulation produced by PESP and insensitive to changes in preload; however, the MSVR varied directly with increases in afterload. The data are summarized in figures 3 and 4.

Discussion

The two principal findings of this study are (1) the MSVR obtained from a single ventricular beat is an index of inotropic state that is insensitive to changes in myocardial length but is sensitive to changes in afterload, and (2) when examined over a range of end-systolic loads, inotropic stimulation increases fiber Emax without altering the extrapolated Vo.

Estimation of contractile function in chronically overloaded ventricles has been difficult because of the unavailability of a load-independent index of contractile function. Hemodynamic parameters measured during the preejection phase of contraction, such as the maximum left ventricular dP/dt, are sensitive to alterations in preload. Ejection-phase parameters such as ejection fraction and velocity of circumferential fiber shortening (Vcf) are sensitive to alterations in afterload. \(^{14, 15}\) Emax, based on the relationship between pressure and volume at end-systole, has recently gained acceptance as an index that is sensitive to inotropic state and relatively insensitive to loading conditions. \(^{1-3}\)

Ventricular afterload can be well characterized by impedance spectra \(^{16}\) that relate instantaneous pressure to instantaneous flow. Impedence, however, does not take into account the interrelationship between ventricular wall thickness, chamber dimensions, and pressure that may affect load at the myocardial fiber level. \(^{4}\) Thus, end-systolic or other indexes of contractile state derived with the use of pressure as a measure of afterload may be normal or higher than normal in hypertrophied ventricles when contractile performance per unit mass of myocardium is actually depressed. \(^{17}\) For this reason, stress-volume relationships are preferred to pressure-volume relationships for use in the comparison of contractile state between ventricles having different thickness-dimension ratios.

Although the end-systolic pressure-volume relationship has been evaluated extensively, there are few reports regarding the influence of inotropic changes on the end-systolic stress-volume relationship. Positive inotropic interventions generally produce an increase in slope but no change in the Vo when pressure is used as a measure of end-systolic load. However, when stress has been used as a measure of load, an increase in Vo with no significant change\(^{6}\) or even an increase\(^{10}\)
in slope has been noted in ventricles in which there is chronic overload hypertrophy, suggesting a shift in the stress-volume relationship to larger volumes with depression of the inotropic state. Borow et al.19 have likewise shown a parallel shift in the end-systolic stress-dimension relationship, with a decrease in end-systolic diameter, for any stress, after short-term inotropic intervention in humans. Weber et al.20 demonstrated alteration of the slope of the force-length relationship in the isolated dog heart with an indeterminate change in the length intercept. The present data indicate that the stress-volume relationship responds to inotropic stimulation, as does the pressure-volume relationship, with an increase in fiber Emax and no significant change in Vo.

The significance of the increase in Vo that occurred after infusion of dextran-nitroprusside in our study is uncertain, but may be related to the inverse correlation of Vo with resistance noted by Maughan et al.,21 who studied pressure-volume relationships in excised canine ventricles connected to a servopump system. These investigators observed deficits in pressure for any given end-systolic volume (i.e., a parallel shift to the right) for beats with large end-diastolic volumes and low resistances compared with those with smaller end-diastolic volumes at higher resistances. The viscoelastic property of muscle, termed creep, may possibly account for such parallel shifts at a constant inotropic state in their study21 and in ours.

Determination of Emax requires repeated measurements of end-systolic ventricular volume over a wide range of systolic pressures. This is difficult in patients in whom hemodynamics are already abnormal, particularly those with critical aortic stenosis.22 Some investigators have therefore used either ventricular pressure or wall stress and ventricular volume at end-systole under basal conditions as a practical alternative
to measuring Emax in disease states associated with abnormal ventricular size and loading conditions.\textsuperscript{7-9} The ratios of pressure to volume\textsuperscript{23} or stress to volume\textsuperscript{24} at end-systole have been presumed, but not proven, to be sensitive to contractile state and independent of preload and afterload. Others\textsuperscript{25} have used the slope of the relationship of stress to volume during late systole for a single beat to estimate contractile state, but this relationship is affected by afterload.\textsuperscript{26} The results of our animal studies demonstrate that, although MSVR is unaltered by short-term changes in preload and is sensitive to short-term inotropic interventions, this ratio also changes in direct proportion to short-term changes in afterload. This is illustrated in figure 5, which also illustrates that the magnitude by which MSVR underestimates fiber Emax depends both on the value of afterload and the magnitude of Vo, since MSVR assumes Vo to be zero.

Thus, a reduced MSVR could be the result of either a depressed inotropic state or reduced afterload. For example, in patients with conditions such as acute mitral regurgitation, MSVR could be depressed as a result of reduced afterload despite the presence of a normal inotropic state. Conversely, increased afterload in patients with decompensated aortic stenosis or regurgitation could partially mask the effects of impaired inotropic state on the MSVR ratio. However, because the computation of ventricular stress provides a means to normalize for abnormal wall thickness and chamber dimensions, this preload-independent index may more accurately assess contractile state in subjects with chronically overloaded ventricles than do traditional indexes of contractility, providing that afterload is not significantly altered from normal.

**Limitations of the study.** A potential pitfall in the use of the stress-volume relationship to estimate contractile function is related to selection of the time in the cardiac cycle during which it is measured. Several definitions of end-systole have been proposed. The time at which ventricular volume reaches a minimum has been traditionally used; however, Sagawa\textsuperscript{1} and Maughan et al.\textsuperscript{27} have noted that coincidence of end-ejection, as indicated by minimum ventricular volume or dicrotic notch, with maximal elastance is circumstantial. These investigators have recently derived Emax using the point in each cardiac cycle at which the pressure-volume ratio reaches maximum\textsuperscript{23} as an alternative to searching pressure-volume regression lines at frequent intervals during the cardiac cycle for the maximum value.\textsuperscript{1} Computer analysis of stress-volume loops in our dogs usually showed that this point in each cardiac cycle very nearly coincided in time with the time of fiber Emax for the series of loops. However, in a few animals it was noted that, when impedance to ejection was markedly reduced by nitroprusside, the MSVR for the loops with the lowest load occurred more nearly the onset of ejection than the end of ejection. As can be seen in figure 5, the rapid decrease in stress during ejection produced by nitroprusside caused the stress-volume ratio to be slightly greater at a time earlier in the loop than at the time of Emax or end-ejection. In this situation, the stress-volume ratio at end-ejection\textsuperscript{9} would be lower, and underestimate fiber Emax by a greater amount, than would MSVR.

Pure alterations in myocardial length, which has been termed preload, are difficult to produce in situ because of the alterations in stroke volume and load (or afterload) that result. We attempted to minimize increases in afterload that accompany increases in preload by using nitroprusside so that the influence of a

![FIGURE 5. Fiber Emax and Vo as described in the methods section. MSVR for each loop fell very close to the regression line. With nitroprusside-induced reduction in afterload, stress fell rapidly during ejection so that for some beats, such as the one designated by the open circle, the MSVR was found earlier during systole.](http://circ.ahajournals.org/doi/fig/10.1161/01.CIR.41.3.652)
relatively pure length alteration on MSVR could be examined. Likewise, an increase in afterload results in an increase in end-diastolic length if preload reserve has not already been exhausted. Thus, we were unable to produce pure alterations in afterload, but since relatively pure changes in preload had no significant effect on MSVR, it can be assumed that the increase in MSVR with aortic constriction was a result of augmented afterload.

A variety of methods have been used for measuring ventricular volume. Isolated heart preparations probably allow the most accurate determination of ventricular volume. Area-length methods of analysis of radiographic images and minor-axis measurements from M mode echocardiograms have been used extensively in humans. Although the technique based on sonomicrometric measurement of left ventricular major and minor axes used in the present study has been recently validated, the computation of volume with an elliptical model is probably less accurate than methods in which the excised heart is used, since the latter does not require such geometric assumptions. However, ultrasonic techniques have the advantage of allowing continuous measurements of cardiac dimensions in situ without the undesirable effects of contrast agents.

In summary, the MSVR measured from a single ventricular beat is sensitive to the inotropic state and is insensitive to preload; however, the sensitivity of this index to afterload limits its usefulness as a practical index of contractile function. The slope of the end-systolic stress-volume relationship, or fiber Emax, which is increased by inotropic stimulation, accounts for varied afterload over multiple beats, and is therefore a more reliable measure of contractile function than the MSVR when myocardial load is abnormal.

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References

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