The development of the entire end-systolic pressure-volume and ejection fraction–afterload relations: a new concept of systolic myocardial stiffness

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ABSTRACT  In this study we introduce a new concept of systolic myocardial stiffness that extends the Suga-Sagawa maximum ventricular elastance concept to the myocardium. End-systole is defined as the time of maximum systolic myocardial stiffness (max Eav), which we examined for its load independence and sensitivity to changes in the inotropic state and to heart rate. Seven adult mongrel dogs were instrumented with ultrasonic crystals for measurements of long and short axes and left ventricular wall thickness, and a high-fidelity micromanometer was inserted for measurement of left ventricular pressures. Preload and afterload were altered by inferior vena cava occlusion, nitroprusside, angiotensin II, atropine, propranolol, and various combinations with propranolol. End-systolic stress-strain relations (slope: max Eav) were linear in all seven dogs, implying that end-systolic myocardial stiffness is independent of end-systolic stress. Changes in max Eav (for constant preload and afterload) reflected changes in the ejection fraction; max Eav was also insensitive to propranolol and to changes in heart rate over the range from 120 to 180 beats/min. End-systolic pressure-volume relations (ESPVRs), derived analytically from these stress-strain relations, were nonlinear, and estimates of volume at zero stress (V_0) were always positive. On the other hand, ESPVRs obtained on the basis of the Suga-Sagawa maximum ventricular elastance concept, were linear, and volume at zero pressure (V_{OP}) estimated by linear extrapolation was negative in one case. Based on the concept of systolic myocardial stiffness, the slope of the ESPVR varies with end-systolic volume and attains its maximum value (E_{max}) at zero end-systolic pressure. Normalization of E_{max} with V_{OP} demonstrated a close relationship to max Eav. Thus both max E_m and V_{OP} and E_{max} are ideal variables for assessing changes in myocardial contractility when preload and afterload are constant. Furthermore, V_{OP} and max Eav permit development of the entire ejection fraction–afterload relationship for a given preload, thus providing a method for comparing myocardial contractile states between ventricles.


THE END-SYSTOLIC ventricular pressure-volume concept developed by Suga and Sagawa1 continues to be a subject of great interest and controversy. Many of these controversies have been addressed in several review articles2-5 and in recent American Heart Association abstracts (1984, 1985, 1986). Sagawa1 has focused in particular on the inapplicable definitions of end-systole, the problems associated with drugs to vary preload and afterload, reliable estimates of zero stress volume (V_0), and normalization of E_{max} (the slope of the end-systolic pressure-volume relation [ESPVR]).

In this study we introduce the concept of a systolic myocardial stiffness, extending the concept of Suga and Sagawa1 to the myocardium. In particular, the new concept addresses the important question of (1) the linearity of the ESPVR and more reliable methods for estimating V_0, (2) the size dependence and normalization of E_{max}, and (3) the development of a new variable that permits the assessment of myocardial contractility via the ejection fraction–afterload relationship at a given preload.

Methods

Terminology. It is necessary first to define specifically the terms used in this study.
Stress difference (σ). The total stress difference \( \sigma = \sigma_0 - \sigma_r \) = the difference of the circumferential (\( \sigma_0 \)) and radial stress (\( \sigma_r \)) components, which are averaged over the entire cross-section. Global average stresses based on force equilibrium considerations are used, since the various stress formulas currently used by many investigators, have yet to be validated experimentally.

Strain difference (ε). The associated strain difference \( \varepsilon = \varepsilon_0 - \varepsilon_r \) = the difference of the midwall circumferential (\( \varepsilon_0 \)) and radial (\( \varepsilon_r \)) strain components at the equator of an ellipse, the assumed geometry for the left ventricle. The assumption implicit here is that the midwall fiber, which is oriented circumferentially, is representative of the deformational behavior of the left ventricle from a global point of view.

Circumferential midwall natural strain (\( \varepsilon_{0n} \)). Natural strain = \( \varepsilon_{0n} = \log (D_0/D_m) \), where \( D_0 \) is the instantaneous midwall minor diameter of the left ventricle and \( D_m \) is the minor diameter at zero stress (\( \sigma = 0 \)). The natural strain definition is preferred to the Lagrangian strain in the case of large deformations and also permits a simple direct relationship between the strain difference \( \varepsilon \) and \( \varepsilon_{0n} \) (Appendix 1).

Average systolic myocardial stiffness (Eav). Eav = \( \sigma / \varepsilon \) = \( \sigma / K_{0n} \), where \( K_n = (2/3)(2 + D_0^2/L_0^2) \), \( L_0 \) being the midwall long axis. This form for Eav has been chosen because (1) it provides an analogy to \( K_{max} \) (slope of the ESPVR), based on the Suga-Sagawa maximum elastance concept, and (2) it is closely related to the concept of an incremental elastic modulus used previously by Mirsky and Rankin8 in their studies of diastolic myocardial stiffness.

Note that for incompressible materials such as cardiac muscle, it is the stress difference that is directly proportional to myocardial stiffness and the strain difference (Appendix 1). Other formulations for the stress/strain ratio (a measure of myocardial stiffness) may be used, but these do not alter the results to be discussed later.

End-systole. This is the time at which systolic myocardial stiffness attains its maximum value.

Maximum ventricular elastance (Eop). Eop = max(\( P - V_{op} \)), where \( V_{op} \) is the left ventricular volume at zero pressure (P = 0).

Animal preparation. Seven adult mongrel dogs were prepared for this study. Each dog was anesthetized with intravenous sodium pentobarbital (25 mg/kg) and underwent left thoracotomy at the fifth intercostal space with sterile technique. Instrumentations were performed after pericardiectomy as reported elsewhere7,9 and shown in figure 1.

Briefly, a high-fidelity micromanometer (Konigsberg P-7) and a Tygon catheter (1.27 mm id) were inserted into the left ventricular cavity through a stab incision at the apex. A pair of pacing wires was sewn to the right atrial appendage. Three pairs of ultrasonic crystals were used for measurement of left ventricular long and short axes and wall thickness (figure 1). The first pair of crystals (8 mm diameter, 3 MHz) was placed on the epicardial surface of the left ventricular anterior and posterior wall to measure the maximum external minor axis at the level approximately two-thirds from apex to base in the longitudinal direction. One crystal of the second pair was placed in the space between the left atrium and the left sinus of Valsalva, and the other was positioned at the apical dimple for measurement of the external long axis. The third pair of crystals (2 mm in diameter at endocardium and 4 mm in diameter at epicardial surface, 5 MHz) was used to measure the dynamics of left ventricular anterior or posterior free wall thickness. An electromagnetic flow probe (In Vivo Metric, Model NQ Series) was placed around the aortic root to measure the aortic phase flow in order to verify the volume calculation from the dimensional data. An inflatable cuff (Jacobson cuff, Research Parametrix)

![Figure 1. Instrumentation of the canine heart.](http://circ.ahajournals.org/)

was positioned around the inferior vena cava (IVC) to control the venous return. The chest was then closed and the pneumothorax evacuated. All wires and catheters were passed to the back of the dog subcutaneously and brought to the skin below the scapulae. After surgery, an antibiotic (ampicillin 0.6 g/day) was administered for 3 days.

Experimental protocol. Studies were performed at least 1 week after surgery when the dogs were active and healthy. During the study, each dog lay quietly on its right side on the table; when necessary, light sedation (5 to 10 mg of acepromazine) was used subcutaneously. Heart rate was controlled at approximately 120 beats/min with atrial pacing (Medtronic, Model 5330) during the interventions.

After recording of control values, pressure and volume of the left ventricle were altered appropriately by IVC cuff occlusion, nitroprusside (maximum dose 30 to 200 \( \mu \)g/min, average 60 \( \mu \)g/min), atropine, angiotensin II (maximum dose 0.5 to 2.0 \( \mu \)g/min, average 0.9 \( \mu \)g/min), propranolol (1 mg/kg), and various combinations with propranolol (nitroprusside, angiotensin II, phenylephrine, IVC occlusion, atropine). In three of the seven dogs, the hearts were paced over the range from 120 to 180 beats/min. All interventions were started after full recovery from the previous interventions, which were checked with left ventricular pressure and dimension data.

The positions of the crystals, left ventricular weight, and myocardial degeneration were examined at necropsy after the studies.

Data analysis. All signals (figure 2) were recorded on an eight-channel Brush chart recorder with the calibration signals and also on a Hewlett-Packard magnetic tape recorder (Model HP 3955D).

The calibration signals and zero point of pressure, which was set at the level of the right atrium, were checked and recorded frequently during the study. The left ventricular pressure signal of the micromanometer was calibrated at end-diastole and end-systole with that of the fluid-filled manometer system, calibrated with the mercury column. The first derivative of the left ventricular pressure (\( dP/dt \)) was obtained by an active differentiating circuit and calibrated against a triangular wave of known slope. Phasic aortic flow was measured by a Statham Model SP2200 gated sine wave flowmeter.

Data on the tapes were replayed later and digitized at a rate of 200 Hz with a computer system (DEC PDP 11/03). Fifteen
consecutive beats at a steady state during control and during interventions were averaged to eliminate the small variations among the beats. All beats in which the preceding pulse-to-pulse interval deviated more than 100 msec from the preaveraged interval were omitted from data averaging. Three averaged beats were calculated and stored for each intervention.

Left ventricular internal long axis (L) and internal minor axis (D) were calculated at 5 msec intervals over the entire cardiac cycle according to the method of Rankin et al. Left ventricular volume and mass were also calculated every 5 msec with the formulas $V = \pi LD^2/6$ and $VM = 1.05[\pi(L + 1.1h)(D + 2h)^2/6 - V]$.

End-diastole was determined at the time the first derivative of pressure (dP/dt) started its rapid upstroke, and end-ejection was determined at the time the left ventricular volume attained its minimum value between peak (+) and (-) dP/dt. Stroke volume was calculated as the difference of calculated left ventricular volume at end-diastole and end-ejection.

**Theoretical considerations**

**End-systolic stress-strain relations.** The average stress difference $\sigma$ (based on an equilibrium of forces in the circumferential direction) is calculated by

$$\sigma = \sigma_{ls} - \sigma_{es} = \text{PLD/2h}(L + 0.55D + 1.1h) + P/2 \quad (1)$$

where $\sigma_{ls}$ is the average circumferential stress, $\sigma_{es}$ is the average radial stress, $P$ is the left ventricular pressure, and $L$, $D$, and $h$ are the long axis, short axis, and left ventricular wall thickness, respectively. Note that the Rankin model was used for the evaluation of the stress $\sigma_{es}$.

By means of a modification of a method developed by Sugawa et al., the average systolic myocardial stiffness ($E_{av}$), where

$$E_{av} = \sigma/K_m \epsilon = \sigma/K_m \log (D_m/D_{om}) \quad (2)$$

was evaluated iteratively in the following manner:

1. A value for $D_{om}$ was first assumed, and for each intervention $E_{av}$ was evaluated from the onset of systole until it attained a maximum; by definition, this is end-systole.
2. The stress vs log $D_m$ points at these maxima were then plotted, and a new value for $D_{om}$ was obtained by appropriate extrapolation to zero stress. Specifically, both linear and curvilinear regressions were performed, and tests of significance of departure from linearity were conducted.

3. This iterative procedure was continued until $D_{om}$ converged close to a constant value. If in addition, the maximum systolic myocardial stiffness ($E_{av}$) is independent of end-systolic stress, this implies linearity of the end-systolic stress-strain relation ($\sigma_{es}$ vs $\epsilon_{es}$) and is represented in the form:

$$\max E_{av} = (l/K_m) \max (\sigma/\epsilon_0) = (l/K_m) \sigma_{es}/\epsilon_{es}$$

or

$$\sigma_{es} = \max E_{av}(K_m \epsilon_{es}) \quad (3)$$

where $\epsilon_{es} = \log(D_{mes}/D_{om})$ and $e$ denotes the end-systolic state. Thus $E_{av}$ is the slope of the linear stress-strain relation (equation 3) and is analogous to $E_{max}$ (the slope of the ESPVR), based on the Sugawa-Sagawa maximum ventricular elastance concept.

**End-systolic pressure-volume relations based on the maximum stiffness and maximum elastance concepts.** For comparison purposes, two methods were used for the evaluation of the ESPVR and $V_o$. These methods are outlined in detail in Appendix 2. The results are as follows:

$$P_{es} = (K_m \gamma/G) \max E_{av} \log(V_{es}/V_{om}) \quad (4)$$

(maximum systolic stiffness concept)

where $\gamma$ is a curve-fitting parameter and $G$ is a geometric factor, and

$$P_{es} = E_{max}(V_{es} - V_{op}) \quad (5)$$

(maximum elastance concept)

where $E_{max}$ is the slope of this linear relationship.

**Estimation of zero-stress volume and maximum systolic myocardial stiffness based on a single control beat analysis.** In the clinical setting it may not always be possible to employ various drug interventions for altering preload and afterload. It is desirable therefore to develop approximate methods for estimating $V_o$ and max $E_{av}$, and one such method is given in Appendix 2.
Results

Figure 3, A and B, displays the end-systolic stress vs log Dm relations for one of the experiments (No. 1), without (A) and with (B) propranolol. F tests\textsuperscript{15} indicated that these relationships showed no significant departure from linearity. Extrapolation of these relationships yielded Dm (midwall diameter at zero stress) and hence the associated end-systolic stress-strain relations (figure 3, C).

End-systolic stress-strain relations with and without propranolol are shown in figure 4 for four additional experiments (Nos. 2 to 5) and in figure 5 for two other experiments (Nos. 6 and 7) with or without propranolol. In all cases, the F test demonstrated no significant departure from linearity, thus validating the hypothesis that end-systolic myocardial stiffness (Eav)\textsubscript{es} is independent of end-systolic stress over wide ranges of stress. A further validation of this hypothesis is presented in table 1, which displays the end-systolic myocardial stiffness vs end-systolic stress relations [(Eav)\textsubscript{es} vs \(\sigma_{es}\)] based on endocardial (\(\varepsilon_e\)) and midwall strain (\(\varepsilon_m\)) formulations, where \(\varepsilon_e = K_e \log (D/Do)\) and \(\varepsilon_m = K_m \log (D_m/D_{om})\).

No significant relationships were observed in all cases between (Eav)\textsubscript{es} and \(\sigma_{es}\). Similar analyses also demonstrated no significant relationship between end-systolic myocardial stiffness (Eav)\textsubscript{es} and preload (end-diastolic stress).

The effects of heart rate on the end-systolic stress-strain relations for three experiments (Nos. 1, 4, and 5) are displayed in figure 6. No significant difference between the slopes at heart rates from 120 to 180 beats/min were observed in all three cases.

The end-systolic pressure-volume relation (equation 4), derived analytically from the end-systolic stress-strain relation (equation 3), is displayed for experiments 1 and 2 in figure 7, together with the ESPVR based on the Suga-Sagawa concept. The experimental values of pressures and volumes shown in figure 7 correspond to the points of maximum ventricular elastance, i.e., max [P/(V – Vop)]. Table 2 displays the ESPVR and E\textsubscript{es} for all experiments based on the Suga-Sagawa concept of maximum ventricular elastance. Linearity of these relationships was observed in all cases.

Table 3 lists the values of the zero-stress volumes V\textsubscript{om}, V\textsubscript{oe}, V\textsubscript{op}, and V\textsubscript{es} based on midwall strain, endocardial strain, maximum ventricular elastance, and a

![FIGURE 3. End-systolic stress vs log Dm and associated stress-strain relations with and without propranolol. The end-systolic stress vs log Dm relations without (A) and with (B) propranolol are linear. Afterload was altered from control (C) by nitroprusside (NP), angiotensin II (AT), and inferior vena cava occlusion (IVC) and by each in combination with propranolol (Pr) at constant heart rates (HR) of 120 and 140 beats/min. Linear extrapolation yielded the midwall diameter Dm\textsubscript{es} at zero stress. Dm\textsubscript{es} = end-systolic midwall diameter. C. The end-systolic stress-strain relations without and with propranolol were obtained from the relations in panels A and B with Dm as the reference length. Linearity of these relations imply that end-systolic stiffness (slope of these relationships: max Eav) is independent of end-systolic stress (\(\sigma_{es}\)). There was no significant difference in the slopes with and without propranolol. Strain difference \(\varepsilon_{es} = K_m \log (D_{mes}/D_{om})\). See text for details.](http://circ.ahajournals.org/content/13/3/346.full)
single-beat analysis, respectively. Figure 8 displays the close relationship between the zero stress volumes based on single- and multiple-beat analyses ($V_a$ vs $V_{om}$). The ESPVR based on single-beat analyses are shown in figure 9 for experiments 1 and 2.

**Discussion**

Ever since Suga and Sagawa proposed their concept of the end-systolic pressure-volume relation, many attempts have been made to apply the concept in the clinical setting, with only minimal success. This lack
TABLE 1
End-systolic stiffness-stress relations based on endocardial and midwall strain models

<table>
<thead>
<tr>
<th>Experiment No.</th>
<th>n</th>
<th>Midwall stiffness-stress relations</th>
<th>r</th>
<th>Endocardial stiffness-stress relations</th>
<th>r</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>(Eav)$<em>{es}$ = 968 + 0.134 $\sigma</em>{es}$</td>
<td>.081</td>
<td>(Eav)$<em>{es}$ = 517 - 0.192 $\sigma</em>{es}$</td>
<td>.186</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>(Eav)$<em>{es}$ = 1042 - 0.048 $\sigma</em>{es}$</td>
<td>.020</td>
<td>(Eav)$<em>{es}$ = 567 - 0.098 $\sigma</em>{es}$</td>
<td>.078</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>(Eav)$<em>{es}$ = 1016 + 0.088 $\sigma</em>{es}$</td>
<td>.039</td>
<td>(Eav)$<em>{es}$ = 535 + 0.048 $\sigma</em>{es}$</td>
<td>.040</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>(Eav)$<em>{es}$ = 985 + 0.293 $\sigma</em>{es}$</td>
<td>.153</td>
<td>(Eav)$<em>{es}$ = 539 + 0.060 $\sigma</em>{es}$</td>
<td>.058</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>(Eav)$<em>{es}$ = 1204 + 0.066 $\sigma</em>{es}$</td>
<td>.043</td>
<td>(Eav)$<em>{es}$ = 617 + 0.00212 $\sigma</em>{es}$</td>
<td>.003</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>(Eav)$<em>{es}$ = 1626 - 0.951 $\sigma</em>{es}$</td>
<td>.421</td>
<td>(Eav)$<em>{es}$ = 749 - 0.219 $\sigma</em>{es}$</td>
<td>.225</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>(Eav)$<em>{es}$ = 813 - 0.040 $\sigma</em>{es}$</td>
<td>.051</td>
<td>(Eav)$<em>{es}$ = 421 - 0.077 $\sigma</em>{es}$</td>
<td>.128</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>(Eav)$<em>{es}$ = 929 + 0.014 $\sigma</em>{es}$</td>
<td>.009</td>
<td>(Eav)$<em>{es}$ = 459 - 0.014 $\sigma</em>{es}$</td>
<td>.017</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>(Eav)$<em>{es}$ = 1224 + 0.079 $\sigma</em>{es}$</td>
<td>.062</td>
<td>(Eav)$<em>{es}$ = 684 - 0.008 $\sigma</em>{es}$</td>
<td>.010</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>(Eav)$<em>{es}$ = 1536 + 0.063 $\sigma</em>{es}$</td>
<td>.032</td>
<td>(Eav)$<em>{es}$ = 845 + 0.064 $\sigma</em>{es}$</td>
<td>.053</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>(Eav)$<em>{es}$ = 1380 - 0.615 $\sigma</em>{es}$</td>
<td>.255</td>
<td>(Eav)$<em>{es}$ = 691 - 0.522 $\sigma</em>{es}$</td>
<td>.306</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>(Eav)$<em>{es}$ = 542 - 0.029 $\sigma</em>{es}$</td>
<td>.026</td>
<td>(Eav)$<em>{es}$ = 230 - 0.109 $\sigma</em>{es}$</td>
<td>.251</td>
</tr>
</tbody>
</table>

(Eav)$_{es}$ = end-systolic stiffness (g/cm²); $\sigma_{es}$ = end-systolic stress (g/cm²); W/O Pr = without propranolol; W/Pr = with propranolol.

of success is attributable to many factors, including (1) the assumption of linearity of the ESPVR outside the physiologic range, thus bringing into question the constancy of $E_{max}$, (2) the size dependence of $E_{max}$, hence limiting its usefulness for comparison purposes, especially in pathologic states of dilated ventricles, and (3) the resulting negative values obtained for $V_o$ in many clinical and animal studies as a consequence of assumption 1. Furthermore, development of simple ratios such as $(P/V)_{max}$, (stress/volume)$_{max}$, etc., should be discouraged. These ratios are not only size dependent but are also based on single-point evaluations.
which cannot describe completely a phenomenon that should be represented by a more involved relationship. In this study we sought to address these problems, which are now discussed individually in more detail.

Linearity of the end-systolic pressure-volume and stress-strain relations. The present studies indicate that over

the ranges of data actually obtained, both the ESPVR and the end-systolic stress-strain relations are linear. How then does one reconcile this apparent contradiction of a linear ESPVR based on the Suga-Sagawa concept with nonlinearity of the ESPVR (equation 4) obtained indirectly from the stress-strain relation? First, the rationale for assuming linearity of the stress-

### TABLE 2
End-systolic pressure-volume relationships and $E_{\text{max}}$ based on maximum elastance concept

<table>
<thead>
<tr>
<th>Experiment No.</th>
<th>n</th>
<th>ESPVR</th>
<th>$E_{\text{max}}$ (mm Hg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8</td>
<td>$P_{es} = 8.7$ ($V_{es} - 6.1$)</td>
<td>.982 8.7</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>$P_{es} = 6.8$ ($V_{es} - 4.2$)</td>
<td>.956 6.8</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>$P_{es} = 3.7$ ($V_{es} - 7.0$)</td>
<td>.952 3.7</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>$P_{es} = 3.2$ ($V_{es} - 3.8$)</td>
<td>.938 3.2</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>$P_{es} = 4.0$ ($V_{es} - 22.7$)</td>
<td>.995 4.0</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
<td>$P_{es} = 4.1$ ($V_{es} - 22.9$)</td>
<td>.985 4.1</td>
</tr>
<tr>
<td>7</td>
<td>8</td>
<td>$P_{es} = 5.9$ ($V_{es} - 8.0$)</td>
<td>.990 5.9</td>
</tr>
<tr>
<td>8</td>
<td>8</td>
<td>$P_{es} = 5.8$ ($V_{es} - 9.0$)</td>
<td>.972 5.8</td>
</tr>
<tr>
<td>9</td>
<td>7</td>
<td>$P_{es} = 5.8$ ($V_{es} - 8.4$)</td>
<td>.947 5.8</td>
</tr>
<tr>
<td>10</td>
<td>7</td>
<td>$P_{es} = 7.3$ ($V_{es} - 16.9$)</td>
<td>.953 7.3</td>
</tr>
<tr>
<td>11</td>
<td>5</td>
<td>$P_{es} = 5.5$ ($V_{es} - 8.3$)</td>
<td>.980 5.5</td>
</tr>
<tr>
<td>12</td>
<td>6</td>
<td>$P_{es} = 1.8$ ($V_{es} + 13.4$)</td>
<td>.932 1.8</td>
</tr>
</tbody>
</table>

$P_{es} = \text{end-systolic pressure (mm Hg)}$; $V_{es} = \text{end-systolic volume (ml)}$; $E_{\text{max}} = \text{maximum slope of the ESPVR}$; other abbreviations as in Table 1.

### TABLE 3
Zero-stress volume based on end-systolic stiffness and maximum elastance concepts

<table>
<thead>
<tr>
<th>Experiment No.</th>
<th>$V_{om}$</th>
<th>$V_{oe}$</th>
<th>$V_{om}$</th>
<th>$V_{op}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8</td>
<td>10.3</td>
<td>11.5</td>
<td>6.1</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
<td>11.7</td>
<td>11.9</td>
<td>9.8</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>18.2</td>
<td>18.6</td>
<td>17.8</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>19.5</td>
<td>19.8</td>
<td>22.5</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>30.8</td>
<td>30.7</td>
<td>26.1</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
<td>32.2</td>
<td>31.9</td>
<td>28.3</td>
</tr>
<tr>
<td>7</td>
<td>8</td>
<td>13.6</td>
<td>13.6</td>
<td>10.6</td>
</tr>
<tr>
<td>8</td>
<td>8</td>
<td>14.8</td>
<td>14.8</td>
<td>11.3</td>
</tr>
<tr>
<td>9</td>
<td>7</td>
<td>17.7</td>
<td>17.6</td>
<td>14.3</td>
</tr>
<tr>
<td>10</td>
<td>7</td>
<td>21.2</td>
<td>21.2</td>
<td>18.7</td>
</tr>
<tr>
<td>11</td>
<td>5</td>
<td>17.5</td>
<td>17.5</td>
<td>13.2</td>
</tr>
<tr>
<td>12</td>
<td>6</td>
<td>12.8</td>
<td>12.6</td>
<td>13.6</td>
</tr>
</tbody>
</table>

$V_{om}$, $V_{oe}$, $V_{op}$ = zero stress-volumes based on midwall strain, endocardial strain, single-beat analysis, and maximum elastance concept, respectively (ml); n = sample size.
strain relation outside the range of the measured data is based on the observations in most cases that extrapolation takes place over a shorter relative range compared with that for the end-systolic pressure-volume data. Second, physiologic considerations dictate that $V_o$ cannot attain negative values, which are obtained only when linear extrapolation of the ESPVR has been performed.$^{16-18}$ Furthermore, linearity of the end-systolic stress-strain relations has been suggested in the earlier studies by Ison-Franklin et al.$^{19}$ and Marsh et al.$^{20}$ and more recent studies by Sagawa et al.$^{21}$ and Suga et al.$^{22}$ have demonstrated nonlinearity of the ESPVR at high end-systolic volumes.

As observed in table 3, values of $V_{op}$ (obtained by linear extrapolation) are markedly lower than values of $V_o$ obtained by the present methods. Underestimation of $V_o$ could lead to artificial nonlinearity of the stress-strain relation. In fact, a nonlinear end-systolic stress-strain relation would imply a load dependence of myocardial stiffness max $E_{av}$, and since this is directly related to ventricular $E_{max}$, it would contradict the result that ventricular $E_{max}$ is independent of load. The close relationship between max $E_{av}$ and $E_{max}$ is evaluated below.

The nonlinear pressure-volume relation given by expression 4 exhibits several interesting properties. First, for values of end-systolic volume ($V_{es}$) close to $V_{om}$, the logarithmic term may be approximated by $\log (V_{es}/V_{om}) \sim (V_{es} - V_{om})/V_{om}$. Hence, $P_{es} \sim [(K_{m} \gamma \max E_{av}/V_{om} + (\alpha + \beta V_{om})) (V_{es} - V_{om}) = E_{max} (V_{es} - V_{om})]$, where $E_{max}$ is the absolute maximum value of the slope of the ESPVR and occurs at zero stress. Since $E_{max}$ reflects changes in the inotropic state and $V_{om}$ remains constant during these changes,$^{23}$ the result implies that max $E_{av}$ reflects changes in myocardial contractility. This is discussed in more detail later.

Second, if $V_{es} < V_{om}$, the pressures become nega-

---

**FIGURE 7.** End-systolic pressure-volume relations based on the maximum myocardial stiffness and maximum ventricular elastance concepts. The solid curve represents the relation obtained from the maximum myocardial stiffness concept and is clearly nonlinear. The dotted straight line is the end-systolic pressure-volume relation obtained from the maximum ventricular elastance concept. The isolated points represent the measured pressures and volumes at the time of maximum ventricular elastance. $V_{om}$ = zero stress-volume obtained from the present theoretical model; $V_{op}$ = zero stress-volume obtained by linear extrapolation of the maximum elastance points. Linear extrapolation may lead to spurious results for $V_{op}$, as occurred in experiment 7. Abbreviations as in previous figures.

**FIGURE 8.** Zero stress-volume based on a single beat ($V_{os}$) vs zero stress-volume based on multiple beats ($V_{om}$). $V_{es}$ was obtained from extrapolation of curve-fits to data from peak stress to the first minimum volume point. Note the closeness of these estimated values to the dotted line of identity.
tive, a result in qualitative agreement with the studies by Sunagawa et al.,24 who demonstrated that the end-diastolic and end-systolic pressure-volume curves converge at pressures between −15 and −20 mm Hg (see also figure 1 of ref. 3).

Size and weight dependence of Emax. In earlier studies by Mirsky et al.,25 an expression for diastolic ventricular stiffness (dP/dV) was obtained in the approximate form dP/dV ≈ Einc/V (1 + V/Vo), where Einc is the incremental myocardial stiffness, V is the cavity size or volume, and Vo is the left ventricular wall volume. This expression is also valid in late systole, and since Emax represents the maximum slope of a pressure-volume relation, it may be identified with dP/dV, which is readily seen to be inversely related to size V. This theoretical result has been confirmed in animal studies by Bogen et al.,26 who obtained a hyperbolic inverse relationship between Emax and body weight. Similar results have also been obtained for Emax vs left ventricular weight relations by Belcher et al.27 in their studies of 15 dog hearts. Furthermore, clinical studies in pediatric patients show that a child’s normal left ventricle has a greater Emax than an adult normal left ventricle.

Max Eav is sensitive to changes in myocardial contractility. The present results confirm that max Eav (slope of the end-systolic stress-strain relation) is independent of preload and afterload. It now remains to examine its sensitivity to changes in the inotropic state from both a theoretical and experimental point of view.

In Appendix 3 a relationship between the ejection fraction at end-systole (EFo) and max Eav has been derived for constant preload and afterload. Figure 10 displays these relationships for experiments 1 and 2, and it is readily observed that increases/decreases in max Eav result in increases/decreases in the ejection fraction at constant preload and afterload.

The question of the effects of propranolol on the inotropic state has been the subject of much controversy.29-31 The present studies indicate that max Eav appears to be insensitive to propranolol, although there is a tendency for max Eav to increase with infusion of propranolol. Clinical studies indicate a close inverse relationship between the ejection fraction at zero afterload (EFo) and max Eav. This result is consistent with those obtained with propranolol in the present studies where it is observed that increases in max Eav are associated with decreases in EFo. Furthermore, since...
preload increases with propranolol, these results imply that propranolol has a mild negative inotropic effect. Thus max Eav presents as an ideal candidate for assessing changes in myocardial contractility.

**Effects of heart rate on max Eav.** Over the range in heart rate from 120 to 180 beats/min, max Eav was unaffected; however, there was a tendency for max Eav to increase with increases in heart rate. These results are consistent with those of Maughan et al., who observed no marked effects of heart rate on E_max.

**Normalization of E_max.** The lack of an appropriate normalization of the variable E_max has limited its clinical value, and present attempts at normalization have met with little success. As Sagawa has stated, there is no rationale for employing body surface area even though it is widely used by cardiologists. Caution must also be exercised in the use of left ventricular mass as a normalization variable, since recent studies indicate no significant relationship between E_max and left ventricular mass in pressure overload hypertrophy. Noble suggested the simultaneous consideration of V_o with E_max in providing more useful information. Following this suggestion, Suga et al. examined the variable V_o E_max on a theoretical basis but were unable to explain to their satisfaction the “apparent contradictions” stemming from their analyses. In particular, when they applied their theoretical model to clinical data obtained by Grossman et al., they observed that V_o E_max attained the highest values in patients with heart failure. This observation may indeed be true, since it implies that these ventricles would be operating on the flat portion of the E_max vs max Eav curves (figure 10), hence exhibiting diminished contractile reserve.

An alternative approach to the normalization problem is a modification of that used by Suga et al., i.e., the development of the normalized chamber stiffness–pressure relationships V_es (dP_es/dV_es) vs P_es using expression 4. Thus comparison between ventricles can be made at common levels of pressure. In particular, at zero pressure (P_es = 0) the normalized ventricular stiffness VdP/dV is expressed in terms of maximum systolic stiffness (max Eav) by the relation

\[ V_{om}(dP_{es}/dV_{es})_0 = V_{om}E_{max} = K_m \gamma \max Eav/(\alpha + \beta V_{om}) \]

We thus observe the close relationship between V_om E_max and max Eav. Generally the factor (\alpha + \beta V_{om}) is close to unity for normal dog hearts, but it may attain higher values in dilated ventricles, in which case max Eav may be more sensitive than V_om E_max.

**Ejection fraction–afterload relationship as an assessment of the myocardial contractile state.** The ejection fraction–afterload relationship has been widely used by cardiologists for assessing the myocardial contractile state. However, its use has been limited in the clinical setting for comparison purposes because ejection fraction is preload dependent and single-point measurements obtained from different patients have been used in the development of the relationship.

The present concept of systolic myocardial stiffness not only permits comparisons to be made at common levels of preload and afterload but also enables one to develop the entire ejection fraction–afterload relationship (EF es − σ es). Figure 11 displays these relationships based on both the maximum elasstance and maximum stiffness concepts (Appendix 4). Although the morphology of these curves differs at low and high afterload, there is good agreement over the physiologic ranges of ejection fraction and afterload. It is of interest to note that the convex shape of the curve based on the present concept is similar to the pump function curve (mean systolic pressure vs cardiac output) obtained by Elzinga and Westerhof. However, further studies are needed to resolve the differences that occur at the high and low afterloads.

**Limitations of the analyses.** There are several limitations to the present study that must be addressed:

1. The estimation of V_o is very important and will require more detailed study in future investigations, since it plays a major role in the evaluation of EF_o (ejection fraction at zero afterload) and on the question of linearity of the stress-strain relation. However, the present method always yields positive values for V_o, in contrast to negative values obtained occasionally by linear extrapolation.

2. The theoretical model described here assumes that stress is a function of strain (volume) alone. Although first-order (“viscous”) and second-order (“inertial”) effects appear not to influence end-systolic stiffness levels seriously, such effects need to be considered if we wish to evaluate the time course of stiffness more accurately.

3. End-systolic stiffness (max Eav) has been shown to be load independent in the normal conscious dog, but this may not be the case in pathologic states. Thus if the end-systolic stress-strain relation is nonlinear, changes in the inotropic state will need to be examined by comparing stiffnesses at common stress levels. On the other hand, it will still be possible to derive the end-systolic pressure-volume relations, obtain estimates to V_o, and also develop the entire ejection fraction–afterload relationships.

4. The possibility always exists that results from theoretical studies could be model dependent. This question has been addressed in this study by the use of...
several different formulations for the myocardial stiffness analyses and the results have been shown to be similar in each case. In particular, analyses were also conducted with endocardial and midwall Lagrangian strain definitions.

(5) Experimentally, the major problem relates to the assessment of ventricular volumes during systole. Although the flowmeter could not be calibrated with absolute flow, the relative changes of stroke volume derived from the flowmeter and from the dimensional data were well correlated.7,8

In summary, in this study we have described a new approach to the evaluation of the end-systolic pressure-volume relation, enabling V₀ (the zero stress volume) to be estimated with more reliability. A new variable max Eav is proposed as an ideal candidate for assessing changes in myocardial contractility, since it has been shown to be load independent and sensitive to changes in the inotropic state. Furthermore, estimates of V₀ and max Eav enable one to evaluate the entire EFₘ₀ - σₘ₀ relation at a given preload, thus providing a more reliable approach for comparison of contractile states. If the assumptions employed here are valid in pathologic states, evaluation of the ESPVR and EFₘ₀ - σₘ₀ relation may be obtained from a single control beat analysis, thus alleviating the need for drug interventions.

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**Appendix 1**

**Development of an expression for average systolic myocardial stiffness (Eav).** From elasticity theory, it can be shown6 that an arbitrary state of stress is expressible as the sum of a hydrostatic and a deviatoric stress. As the name implies, the hydrostatic stress is similar to the state of stress in a body submerged in a fluid at rest; that is, stresses are the same on all planes. The deviatoric stress is that portion of the stress that remains after subtracting the hydrostatic stress. Similarly, the state of strain may be decomposed into a hydrostatic (volumetric) strain and a deviatoric strain, the former being a measure of the change in volume per unit volume and the latter a measure of the change in shape.

For an incompressible material such as cardiac muscle, all the strain is deviatoric (since volumes are preserved), thus the deviatoric stress alone is determined by the strain. In particular, in an r, θ, φ coordinate system, the total stress components σᵣ may be expressed in terms of the strain components εᵣ as:

\[
\sigma_r = -P_\text{ho} + (2/3)E \varepsilon_r
\]

\[
\sigma_\theta = -P_\text{ho} + (2/3)E \varepsilon_\theta
\]

\[
\sigma_\phi = -P_\text{ho} + (2/3)E \varepsilon_\phi
\]

where P_\text{ho} is a uniform hydrostatic pressure, E is elastic stiffness, and r, θ, and φ are, respectively, the radial, circumferential, and meridional coordinates.

From equation 1.1 it is observed that the differences of the stress components are independent of the hydrostatic pressure P_\text{ho} and in particular:

\[
\sigma_\theta - \sigma_r = (2/3)E(\varepsilon_\theta - \varepsilon_r)
\]

In the present study, we identify the average systolic myocardial stiffness Eav with E, thus:

\[
Eav = (\sigma_\theta - \sigma_r)/[(2/3)(\varepsilon_\theta - \varepsilon_r)]
\]
The rationale for the choice of natural strain (log l/l₀) in preference to Lagrangian strain (1 - l₀/l) has been discussed previously. Furthermore, it has also been shown that as a consequence of incompressibility, the natural strain components satisfy the condition:

\[(εₐ + ε₀ + εₜ₀) = 0 \quad (1.4)\]

and at the midwall, the strains εсмотреть₀ and εсмотреть are approximated by the expressions:

\[εсмотреть₀ \sim (Dₗ₀^2/Lₘ₀)cₒ₀ \]

and

\[εсмотреть = -εсмотреть₀ - εсмотреть₀ \sim -(1 + Dₗ₀^2/Lₘ₀)cₒ₀ \]

hence

\[εсмотреть₀ - εсмотреть \sim (2 + Dₗ₀^2/Lₘ₀)cₒ₀ \quad (1.5)\]

where Dₗ₀ and Lₘ₀ are, respectively, the midwall short and long axes of an ellipsoid of revolution, the assumed geometry of the left ventricle. Thus the final expression for Eav takes the form:

\[Eav = (σ₀ - σₑ)/(2/3)(εₑ - εₑ) - σ/c = σ/K₉ₐ₀ \quad (1.6)\]

where σ = σ₀ - σₑ; εₑ = (2/3)(εсмотреть₀ - εсмотреть₀); K₉ = (2/3)(2 + Dₗ₀^2/Lₘ₀); and εсмотреть₀ = log (Dₗ₀/Dₘ₀).

**Appendix 2**

End-systolic pressure-volume relations and estimation of zero stress volume V₀ based on maximum stiffness and maximum elastance concepts

**Method 1:** Systolic myocardial stiffness concept. The end-systolic pressure-volume relation was derived analytically from the end-systolic stress-strain relation (equation 3) in the following manner:

(1) Plots of the end-systolic midwall diameter vs volume (Dₘₙₑ s vs V₀) and σₑ/Pₑs vs Vₑs points were first obtained for each intervention.

(2) The resulting plots were then curve-fitted in the form:

\[Dₘₙₑ = A V₀^β; \quad σₑ/Pₑs = G = α + β Vₑs \quad (2.1)\]

where A, γ, α, and β are regression coefficients.

(3) From expression 2.1, the zero stress volume V₀ was estimated in terms of the known extrapolated value for Dₘₙₑ (figure 3) obtained from the relation:

\[Dₘₙₑ = A V₀^β \quad (2.2)\]

Hence, Dₘₙₑ/Dₘ₀ = A V₀/A V₀ = (Vₑs/V₀)γ, and therefore

\[log(Dₘₙₑ/Dₘ₀) = γ log(Vₑs/V₀) \quad (2.3)\]

Thus from expressions 2.1, 2.2, and 2.3 and the stress-strain relation, εₑ₀ = max Eav (Kₑ₀ εₑ₀), the ESPVR takes the form:

\[Pres = σₑ₀/G = (Kₑ₀ G) max Eav - εₑ₀ = (Kₑ₀ max Eav/G) log(Dₘₙₑ/Dₘ₀) = (Kₑ₀ g max Eav/log Vₑs/V₀) \quad (2.4)\]

**Method 2:** Ventricular elastance concept. The direct method for evaluating the ESPVR follows closely that developed by Sunagawa et al.14

(1) A value for V₀ (volume at zero end-systolic pressure) was first assumed, and for each intervention ventricular elastance P(V - V₀) was evaluated from the onset of systole until it attained a maximum value. By definition, this is end-systole.

(2) The pressure vs volume points at these maximal values were then plotted and a new value for V₀ was obtained by linear extrapolation.

(3) This iterative procedure was continued until V₀ converged close to a constant value. If, in addition, the maximum ventricular elastance (Eₑ₀) is independent of end-systolic pressure, this implies linearity of the ESPVR (Pₑs vs Vₑs):

\[max[P(V - V₀)] = Pₑs(Vₑs - V₀) = E_max \quad (2.5)\]

or

\[Pₑs = E_max(Vₑs - V₀)\]

where E_max is the slope of this linear relationship.

Estimation of zero-stress volume and maximum systolic myocardial stiffness based on a single-beat analysis. An approximate method for estimating Vₑs and max Eav is outlined.

(1) An estimate of Vₑs (zero stress volume based on a single control beat) was obtained by curve-fitting the stress-volume data (σ – V) in late systole from peak stress to the first minimum volume point in the form:

\[σ = A_c - B_c V^{−α_c} \quad (2.6)\]

where A_c, B_c, and α_c are regression coefficients. This form was chosen because it is observed from earlier analysis that (1) the stress σ decreases as the volume decreases and (2) the slope dσ/dV = α_c B_c V^{−α_c-1} increases as the volume decreases. Hence V₀ was obtained by extrapolation of this curve-fit to zero stress with the result:

\[A_c - B_c V₀^{−α_c} = 0 \quad (2.7)\]

Obviously other forms of curve-fits could have been chosen to satisfy these characteristics.

(2) Using analyses similar to those described earlier, we obtain the ESPVR in the form:

\[Pres = (Kₑ/G) max Eav log(Vₑs/V₀) \quad (2.8)\]

where the parameters Kₑ, γ, α, and β are obtained from the expressions Dₘₙₑ = C Vₑs; Dₘ₀ = C V₀; Kₑ = (2 + Dₗ₀^2/Lₘ₀); and G = a + b V; and max Eav = (1/Kₑ) max [σ/log(Dₘₙₑ/Dₘ₀)]. Note that a, b, C, and δ are curve-fitting parameters.

**Appendix 3**

Relationship between ejection fraction (Eₑ₀) and maximum systolic stiffness (max Eav) for constant preload and afterload. The equations to determine the Eₑ₀ vs max Eav relationship are:

\[Pres = (Kₑ/γ max Eav) log(Vₑs/V₀) \quad (3.1)\]

\[V_es = (1 - Eₑ₀)Vₑ₀ \quad (3.2)\]

\[σ₀ = σₐf = σₑ₀ - Pₑs/2 = G Pₑs - Pₑs/2 = Pₑs(G - 0.5) \quad (3.3)\]

where σₐf is the average circumferential stress defined here as the constant afterload and Vₑ₀ is the constant end-diastolic volume yielding a constant preload (end-diastolic stress). Note that σ₀ and Pₑs are in the same units (mm Hg).

Hence, elimination of Pₑs and Vₑs from the above equations yields the complex relationship between Eₑ₀ and max Eav:

\[(Kₑ γ max Eav) log[(1 - Eₑ₀)Vₑ₀/V₀] = σₐf G/G - 0.5 \quad (3.4)\]

where

\[G = α + β Vₑ₀ = α + β Vₑ₀(1 - Eₑ₀)\]

**Appendix 4**

Ejection fraction–afterload relationships at constant preload, based on the maximum elastance and maximum stiffness concepts

Maximum elastance concept. The ejection fraction vs after-
load relationship \( (E_{F_0} \text{ vs } \sigma_{st}) \) is determined from the following expressions:

\[
P_e = \frac{E_{max}(V_{es} - V_{op})}{(1 - \sigma_{st})V_{ed}} \\
V_{ed} = (1 - E_{F_0})V_{ed}
\]

(4.1)

(4.2)

\[
\sigma_0 = \sigma_{st} = \sigma_{es} - \frac{P_e}{2} = \frac{G P_{es} - P_e}{2} = (G - 0.5)P_e
\]

(4.3)

where the various parameters have been previously defined in the text and in Appendix 3.

Elimination of \( P_e \) and \( V_{es} \) from the above equations yields the complex relationship between \( E_{F_0} \) and \( \sigma_{st} \):

\[
E_{max}[(1 - E_{F_0})V_{es} - V_{op}][\alpha + \beta V_{ed}(1 - E_{F_0}) - 0.5] = \sigma_{st}
\]

(4.4)

where \( V_{ed} \) is a constant.

**Maximum stiffness concept.** A similar analysis (Appendix 3) yields the \( E_{F_0} \) vs \( \sigma_{st} \) relation based on the maximum stiffness concept:

\[
(K_m \gamma max Eav)\log[(1 - E_{F_0})V_{es}/V_{om}] = G\sigma_{st}(G - 0.5)
\]

(4.5)

where \( G = \alpha + \beta V_{es} = \alpha + \beta V_{ed}(1 - E_{F_0}) \) and \( V_{ed} \) is a constant.

Note that the ejection fraction at zero afterload \( (E_{F_0}) \) is given by the formulas \( E_{F_0} = (V_{ed} - V_{op})/V_{ed} \) (elastance concept) and \( E_{F_0} = (V_{ed} - V_{om})/V_{ed} \) (stiffness concept).

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