

Myocardial Stiffness Derived From End-Systolic Wall Stress and Logarithm of Reciprocal of Wall Thickness Contractility Index Independent of Ventricular Size

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The slope of the end-systolic pressure-volume relation (ESPVR) is useful in assessing acute changes in contractile state. However, a limitation of ESPVR is that its slope decreases progressively as ventricular size increases without this change necessarily indicating a change in contractile state. In this respect, an index of contractile function that is independent of ventricular size would have an obvious advantage. The exponential constant (k) of the end-systolic relation between wall stress (σ) and the natural logarithm of the reciprocal of wall thickness [$\ln(1/H)$], $\sigma = Ce^{k \ln(1/H)}$, corresponds to the stiffness constant of the myocardium (k_{SM}), a contractile index that should be independent of ventricular size and geometry. To examine the size independence of k_{SM} , we studied left ventricular k_{SM} during β -blockade (to stabilize inotropic state) in 25 normal dogs with greatly differing ventricular sizes whose end-diastolic volumes ranged from 14 to 82 ml. The k_{SM} was nearly constant (3.6 ± 0.4) over this wide range of end-diastolic volumes and thus was independent of end-diastolic volume. Conversely, ESPVR, also obtained during β -blockade, was closely and negatively correlated to end-diastolic volume ($r=0.92$). To test the ability of k_{SM} to measure changes in contractile state, we altered contractile state pharmacologically. The k_{SM} increased from 3.7 ± 0.5 to 4.8 ± 0.8 ($p < 0.01$) with infusion of dobutamine (after reversal of β -blockade) and decreased to 3.1 ± 0.3 ($p < 0.05$) with inhalation of isoflurane, a negative inotrope, during β -blockade ($p < 0.05$). We conclude that k_{SM} is independent of ventricular size and is sensitive to changes in inotropic state. As such, it should be useful as an index of contractile function. (*Circulation* 1990;82:1352-1361)

Measures of systolic left ventricular stiffness and elastance have been used to measure myocardial contractile state. The slope (E_{ES}) of the end-systolic pressure-volume relation (ESPVR) and modifications of ESPVR are measures of elastance that have been demonstrated to be sensitive indexes of ventricular contractility relatively independent of loading conditions.¹⁻⁶ Unfortunately, E_{ES} depends not only on ventricular contractile state

but also on ventricular size.^{4,7} The slope of the ESPVR is defined as the change in pressure (Δy) divided by the change in volume (Δx). A change in end-systolic pressure of 10 mm Hg in a normal rat may produce a change in end-systolic volume of 0.1 ml ($\Delta y/\Delta x = 100$ mm Hg/ml); an identical change in end-systolic pressure in a normal human might change end-systolic volume by 3 ml ($\Delta y/\Delta x = 3.33$ mm Hg/ml). It is unlikely that innate contractility is 33 times greater in the normal rat than in the normal human. Rather, contractility is probably similar in each normal subject, and the size dependency of E_{ES} creates the large discrepancy. Even within a given species, size variation causes a change in E_{ES} .⁸ Although several attempts to normalize E_{ES} for size have been made,⁷⁻¹² these corrections still remain controversial. An index of contractile function that is independent of ventricular size would have the obvious advantage of not requiring such a correction.

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In this study, we examined a measure of contractility, end-systolic myocardial stiffness, that should be independent of left ventricular size. The method, derived from the regional area-tension relation,¹³⁻¹⁵ calculates regional work per unit volume of myocardium from wall stress (σ) and the natural logarithm of the reciprocal of wall thickness [$\ln(1/H)$].¹⁶⁻¹⁸ As is discussed in "Methods," $\ln(1/H)$ is an expression of myocardial strain. Briefly, strain is defined as the deformation of a material caused by application of a force. It is usually expressed in relation to an unstressed dimension,¹⁹ $\ln(l/l_0)$, or area,¹³ $\ln(A/A_0)$, and is a dimensionless property. In this study, we assume that the myocardium is incompressible.^{20,21} As such, it has a constant volume, which equals its area (A) times its thickness (H); thus, changes in area are reflected by changes in thickness. As noted above, area strain is defined as $\ln(A/A_0)$. Assuming that the myocardium is incompressible, $\ln(A/A_0)$ can be substituted with $\ln(1/H)/(1/H_0)$ or $\ln(H_0/H)$ (further explained below). Myocardial stiffness is described mathematically as the change in stress ($d\sigma$) divided by the change in strain ($d\epsilon$). By altering stress (σ), one alters strain, thereby deriving the σ , $d\sigma/d\epsilon$ relation (myocardial stiffness), which should reflect contractile state. Because the slope of the σ , $d\sigma/d\epsilon$ relation is defined by increments in σ and $d\sigma/d\epsilon$, extrapolation to zero strain to define the slope is unnecessary. This allows our second key assumption, that $\ln(H_0/H)$ can be substituted by $\ln(1/H)$ as the expression of strain in our stress-strain relation. In our previous work, we used a linear (Hookian) model of stress and strain because we examined both stress and strain at high stress (created by aortic constriction), when the relation tends to be linear.^{16,17,22} Current data in the lower range of stress and strain suggest a curvilinear model is probably more appropriate for biological materials. This relation is expressed as $\sigma = Ce^{k\ln(1/H)}$, where σ is stress, C is a constant, and k is the exponential constant. The constant k reflects myocardial stiffness, k_{SM} , and thus reflects inotropic state.

To examine the size independence of the constant k_{SM} relating end-systolic stress and $\ln(1/H)$, we examined this relation in dogs of greatly varying ventricular size. To examine the sensitivity of this index to contractile state, we changed inotropic state by pharmacological intervention. We also compared this new index to E_{ES} derived from the identical set of beats used for developing the end-systolic σ - $\ln(1/H)$ relation. Furthermore, we examined the σ - $\ln(1/H)$ relation over a wide range of afterloads (stresses) to determine whether the relation was linear or curvilinear and also at different preloads to test for independence of preload.

Methods

Theoretical Background

The σ - $\ln(1/H)$ relation is based on previous studies calculating regional work of the ventricle.^{13,16-18,22} An explanation of this derivation follows.

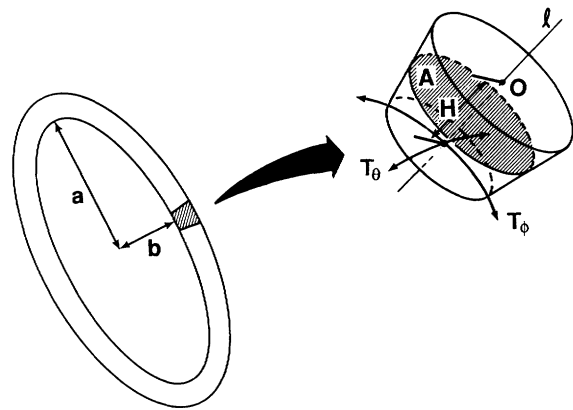


FIGURE 1. Thick-walled ellipsoid model of the left ventricle and schematic illustration of the imaginary section of myocardium that has volume V_m . V_m equals the product of the area (A) and thickness (H) of the section. Although A and H vary during the cardiac cycle, V_m is constant because the myocardium is incompressible. Isotropic wall tension, the average of circumferential and meridional wall tension (T_θ and T_ϕ), is invariant and takes the same value for every direction perpendicular to a straight line perpendicular to the epicardial surface and passing through a selected point O (l). a and b , Major and minor axes of the left ventricle.

Calculation of regional work. The mechanical work done by a region of interest of the ventricular wall is the area under the tension-area curve given by the formula

$$RW = - \int T dA \quad (1)$$

where RW is regional work, T is the isotropic wall tension, A is the area of a regional midwall layer of the ventricle, and the integral is taken over a cardiac cycle.¹³ $T = \text{pressure } (P) \times \text{radius } (r)$; thus, $T \times A = (P \times r) \times r^2 = P \times r^3$ (r^3 has the same units as volume $[V] \approx P \times V$, the more familiar expression of stroke work). The accuracy of RW calculated by this method was validated by Goto et al¹⁴ in excised cross-circulated heart using a volume servo pump system.

In an ellipsoid model of the left ventricle, T calculated at the equator is defined as:

$$T = \frac{1}{2}(T_\theta + T_\phi) \quad (2)$$

where T_θ and T_ϕ are the circumferential and meridional components, respectively, of wall tension at the equator (Figure 1). A relation between T_θ and T_ϕ is given by Laplace's law:

$$P = \frac{T_\theta}{r} + \frac{T_\phi}{R} \quad (3)$$

where r and R are the minor and major radii of curvature of the endocardial surface, respectively, and P is ventricular pressure. The equilibrium of the

forces at the equator in the direction of the long axis yields:

$$T_{\phi} = \frac{rP}{2} \quad (4)$$

From Equations 3 and 4,

$$T_{\theta} = r \left(P - \frac{T_{\phi}}{R} \right) = \left(1 - \frac{r}{2R} \right) Pr \quad (5)$$

As shown in Figure 1, a is the major radius, and b is the minor radius; $r=b$ and $R=a^2/b$. Thus,

$$T_{\phi} = \frac{bP}{2} \quad (6)$$

Substituting for r and R in Equation 5 yields:

$$T_{\theta} = \left(1 - \frac{b^2}{2a^2} \right) bP \quad (7)$$

Therefore, T is expressed as¹³:

$$T = \frac{T_{\theta} + T_{\phi}}{2} = \frac{1}{2} \cdot \left[\frac{bP}{2} + \left(1 - \frac{b^2}{2a^2} \right) bP \right] \\ = \frac{P \cdot b}{2} \left[\frac{3}{2} - \frac{b^2}{2a^2} \right] \quad (8)$$

Because T is isotropic in the plane perpendicular to the radius, it takes the same value for every direction perpendicular to a radius through a point in the ventricular wall.

Normalization of regional work to a unit volume of myocardium. Because larger areas of interest of the myocardium can produce more work than smaller areas of interest, it is necessary to normalize RW to a unit volume of myocardium to compare areas of interest.^{16,17}

Figure 1 shows a schematic illustration of an imaginary section of myocardium that has a volume V_m . V_m equals the product of area (A) and wall thickness (H), measured along a straight line (ℓ) perpendicular to the epicardial surface and passing through a selected point O , of the section:

$$V_m = A \times H \quad (9)$$

Because the myocardium is incompressible, V_m is constant. If we wish to examine RW per unit volume (V_m) of myocardium (RWM), we divide RW by V_m , which equals RW/AH . Thus, $RWM = RW/AH$. Recall Equation 1; thus,

$$RWM = (- \int T dA) / AH \\ = - \int (T/H) (dA/A) \\ = - \int (T/H) (d \ln A) \quad (10)$$

Tension divided by thickness equals wall stress ($T/H = \sigma$); thus,

$$RWM = - \int \sigma d \ln A \quad (11)$$

This equation describes the area surrounded by the σ - $\ln A$ loop. The formula for calculating σ is derived by dividing tension (Equation 8) by thickness:

$$\sigma = \frac{P \cdot b}{2} \left[\frac{3}{2} - \frac{b^2}{2a^2} \right] / H \times 1,332 \text{ dynes/cm}^2 \quad (12)$$

Meaning of $\ln A$ and definition of area strain. The change in $\ln A$ ($d \ln A$), or dA/A , in the σ - $\ln A$ relation expresses a relative change in area ("incremental area strain"). Total area strain (ϵ_i) is given by the following equation:

$$\epsilon_i = \int_{A_0}^A dA/A = \ln A - \ln A_0 = \ln(A/A_0)$$

where A_0 is the area corresponding to a state of zero stress. Definition of A_0 is required to obtain the complete stress-strain relation extrapolated to the x axis. However, A_0 is not required in the analysis of the stiffness relation ($[d\sigma/d\epsilon]$, σ). As noted above, myocardial stiffness is defined as the change in stress ($d\sigma$) divided by the change in strain ($d\epsilon$). This relation examines only incremental changes in stress and strain to define its slope. Thus, extrapolation to A_0 is unnecessary. Therefore, stiffness ($d\sigma/d\epsilon$) is identical using either definition of strain: $\ln A$ or $\ln(A/A_0)$. Thus, A_0 can be omitted, and area strain is defined as

$$\epsilon = \ln A \quad (13)$$

Use of reciprocal wall thickness ($1/H$) instead of area (A). Unfortunately, changes in a regional area of interest of the myocardium are difficult to measure. Conversely, wall thickness and changes in wall thickness are easy to measure by conventional echocardiographic or cineangiographic methods. Thus, substitution of thickness (H) for area (A), if possible, would increase the applicability of the method. The following explains how H can be substituted for A in strain analysis.

The myocardium is incompressible.^{20,21} Thus, the volume of the region of interest (V_m) is constant, even though A and H vary throughout the cardiac cycle as shown in Figure 1. From Equation 9, $A = V_m/H$, so

$$\ln A = \ln(V_m/H) = \ln V_m + \ln(1/H)$$

Because V_m is constant, $d(\ln A) = d \ln(1/H)$. Thus, one can substitute $\ln(1/H)$ for $\ln A$. $\ln(1/H)$ represents strain in the stress-strain relation.

Meaning of the constant (k) of the end-systolic σ - $\ln(1/H)$ relation. The end-systolic σ , $\ln(1/H)$ coordinates, in a constant inotropic state, move along a curvilinear relation as loading conditions change.

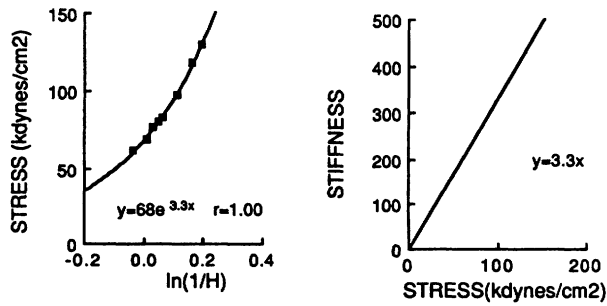


FIGURE 2. Stress–area strain relation (left panel) and stiffness–stress relation (right panel) during volume unloading from a representative dog. The stress–strain relation fits well to an exponential curve expressed as $\sigma=68e^{3.3\ln(1/H)}$ ($r=1.00$), where σ is wall stress and $\ln(1/H)$ is the natural logarithm of the reciprocal of wall thickness, corresponding to area strain. Myocardial stiffness ($d\sigma/d\epsilon$) is a linear function of stress. The slope of this relation ($k_{SM}=3.3$) also is the exponential constant k of the stress–strain relation.

Figure 2 (left panel) shows the end-systolic σ - $\ln(1/H)$ points obtained from several beats in one dog during volume unloading. The end-systolic σ - $\ln(1/H)$ points fit well to an exponential curve expressed as $\sigma=Ce^{k\ln(1/H)}$ ($r>0.995$). k is the exponential constant relating stress to strain. Figure 2 (right panel) shows the end-systolic stiffness–stress relation. Whereas the stress–strain relation is an exponential one, elastic stiffness, $d\sigma/d\epsilon$, is a linear function of stress. As stress increases, stiffness increases (Figure 2, right panel). Here, k , the slope of the end-systolic stiffness–stress relation, is termed the end-systolic stiffness constant of the myocardium (k_{SM}). As contractility increases, stiffness at a given stress increases, and k increases. The derivation of the relation may seem complex, but it should be emphasized that only ventricular pressure, radius, and thickness need to be measured to obtain the relation.

Study Design

We assumed that left ventricular contractile function in healthy dogs during β -blockade (to cancel variations caused by alterations in adrenergic tone) was a normally distributed, relatively constant property. As such, it would vary within a definable range from animal to animal. This variability should not be dependent on ventricular size. Thus, we examined k_{SM} in 25 dogs with widely varying ventricular size to test for the independence of k_{SM} and ventricular size. To maximize size variation, we examined puppies and adult dogs. Although a previous study suggests a plateau in force generation capacity in puppies at high pressure, we limited our study to pressures below the threshold for this limitation.²³ Thus, in the pressure range studied, our puppies and adult dogs were predicted to have similar contractile function.

To test the sensitivity of k_{SM} to changes in inotropic state, k_{SM} was compared in a subset of six animals before and after β -blockade. In a second subset of six animals, sensitivity of k_{SM} to inotropic state was

tested more extensively. The k_{SM} was examined during β -blockade, during β -blockade plus isoflurane anesthesia (isoflurane is a negative inotropic agent),^{24,25} and after reversal of β -blockade plus infusion of dobutamine, a positive inotropic agent.

Because our previous studies performed at high stress levels suggested that the σ - $\ln(1/H)$ relation was linear but the current studies suggested it was curvilinear, in six additional animals we examined the linearity versus curvilinearity of the relation and also the effect of alterations in loading conditions on k_{SM} .

Study Protocol

All experiments were performed in the experimental catheterization laboratory at the Medical University of South Carolina. Eight puppies, 6–8 weeks old and weighing 6.4 ± 2.5 kg, and 17 adult dogs, weighing 22.3 ± 5.0 kg, were studied. Anesthesia was induced with droperidol-fentanyl (Innovar Vet) (0.15 ml/kg i.m.), endotracheal intubation was performed, and animals were mechanically ventilated. Anesthesia was maintained with incremental doses of droperidol-fentanyl together with inhalation of nitrous oxide and oxygen (3:1). This anesthetic combination has been shown to have little effect on inotropic state.²⁶

A 5F pigtail catheter was advanced through the left carotid artery to the left ventricle for recording left ventricular pressure and for performing left ventriculography. A 5F double micromanometer-tipped catheter (SPR419, Millar Instruments, Houston), which had been externally calibrated and balanced, was advanced from the same artery into the left ventricle, where it was matched with the mercury-calibrated pigtail catheter. The Millar catheter was used to record both left ventricular and aortic high-fidelity pressure simultaneously with ventriculography. A 20-mm balloon catheter for the adult dogs and 7F Swan-Ganz catheter for puppies was inserted into the inferior vena cava from the left jugular vein for the purpose of altering load by varying venous return. The animals received esmolol, 0.5 mg/kg/min \times 3 minutes, followed by constant infusion at a rate of 0.3 mg/kg/min intravenously to cause and maintain β -adrenergic blockade, during which contractile function was evaluated.

To obtain baseline ventricular volume and mass, a ventriculogram was performed in the 30° right anterior oblique position at 60 frames/sec. After sufficient time for recovery, the balloon was inflated, causing decreased venous return and a subsequent fall in aortic pressure. Care was taken so that aortic diastolic pressure did not fall below 50 mm Hg, which might have compromised coronary blood flow and contractile function.²⁷ Subsequent balloon deflation produced a beat-by-beat rise in pressure and thus a beat-by-beat change in loading conditions. The balloon was deflated simultaneously with performance of a second ventriculogram and recording of high fidelity pressures, producing the data from which the contractile indexes were derived.

k_{SM} was studied during β -blockade in all 25 animals. To examine whether k_{SM} was sensitive to the reduction in inotropic state produced by β -blockade, k_{SM} also was studied in the resting, anesthetized state without β -blockade and again after β -blockade in a subset of six of the above 25 animals.

To further examine the sensitivity of k_{SM} to contractile state, additional studies were performed in two puppies and four adult dogs. In those animals, after sufficient time for recovery from the second ventriculogram and while β -blockade was maintained, inhalation of 2.5% isoflurane was begun. This negative inotropic anesthetic was used to further depress contractility.^{24,25} Ten minutes later, when depression of left ventricular dP/dt suggested a depression in contractile state, a third left ventriculogram identical to the second was performed. Then, inhalation of isoflurane and drip infusion of esmolol were discontinued. After two half-lives of esmolol had elapsed (18 minutes) and after the effects of isoflurane had dissipated, an intravenous drip infusion of dobutamine (10 μ g/kg/min) was initiated. At a time when dP/dt surpassed the control level, suggesting inotropic state had increased, the last ventriculogram was performed. This ventriculogram also was performed during volume manipulation as described for the second and third ventriculograms.

In a separate set of six experiments using adult dogs, the linearity versus curvilinearity of the σ -ln(1/H) relation was studied over a wider range of stresses than could be developed from the inferior vena cava balloon inflation and deflation technique alone. In this same group of animals, the preload independence and reproducibility of the index also was studied. In these six animals, anesthesia, instrumentation, and β -blockade were introduced as in the previous studies. To increase the range of blood pressure over which the σ -ln(1/H) relation was derived, methoxamine was infused in a dose titrated to produce a steady-state systolic blood pressure of 150–170 mm Hg. The inferior vena cava balloon technique then was used to lower this high pressure, and the σ -ln(1/H) relation was derived as before during balloon deflation, which now produced a large range over which the σ -ln(1/H) was derived. One hour later, while methoxamine was continued, a rapid infusion of 1 l saline was performed. The σ -ln(1/H) relation again was obtained in an identical fashion as before at the peak of volume expansion.

Calculations

Determination of the end-systolic stress–ln(1/H) relation. Left ventricular volumes were calculated using the area-length method.²⁸ Accuracy of this method as used in our laboratory has been documented previously.²⁹ Wall thickness was measured at the mid-anterior wall at the end of diastole. Mass was calculated using the method of Rackley et al.³⁰ Mass and end-diastolic volume were calculated from resting ventriculograms. During subsequent ventriculograms, we assumed that mass remained constant and

used this assumption to calculate changes in wall thickness from measured changes in volume and dimension.³¹ End-systolic pressure was taken from the aortic notch. We recognize that true end-systolic pressure may not always be identical to aortic notch pressure, but we chose aortic notch pressure because it could accurately be defined as a “hard” data point that could be used consistently from beat to beat. The end-systolic volume and dimensions were taken from the frame in which the aortic valve was seen to close.

The σ -ln(1/H) relation was obtained from the end-systolic σ -ln(1/H) coordinates from successive variably loaded beats fit by an exponential model:

$$\sigma = Ce^{k \ln(1/H)} \quad (14)$$

The end-systolic elastic stiffness constant of the myocardium (k_{SM}), which is the exponential constant k , was obtained by solving for k . E_{ES} was determined from linear regression analysis of end-systolic pressure and end-systolic volume taken from the same variably loaded beats used to calculate the end-systolic σ -ln(1/H) relation.

Statistics

All results are reported as mean \pm SD. A two-tailed paired Student's t test was used to compare control k_{SM} with k_{SM} after isoflurane inhalation and to compare baseline k_{SM} with k_{SM} after dobutamine infusion. A two-tailed paired Student's t test also was used to compare k_{SM} under β -blockade with k_{SM} without β -blockade. The r values for k_{SM} assuming a linear fit were compared with r values for k_{SM} , assuming an exponential relation using a paired t test. A paired t test also was used to compare k_{SM} before and after volume expansion. The E_{ES} was determined by linear regression using the least-squares method. A p value less than 0.05 was considered statistically significant. Fitting the end systolic σ -ln(1/H) relation to the general exponential equation

$$\sigma = Ce^{k \ln(1/H)} + B \quad (15)$$

is difficult when the number of variably loaded beats for analysis is small, so we fit the data to both the general form (Equation 15) and to the simple exponential equation $\sigma = Ce^{k \ln(1/H)}$ (Equation 14) in 11 cases in which seven or more data points were available for comparison of the two methods.

Results

End-diastolic volume ranged from 14 to 30 ml in puppies and from 33 to 82 ml in adult dogs. Despite this wide range of ventricular volumes, k_{SM} was nearly constant with a narrow distribution, 3.6 ± 0.4 , and was independent of left ventricular size as shown in Figure 3. Conversely, E_{ES} was closely related to left ventricular size by a logarithmic function ($r=0.92$) as shown in Figure 4.

Figure 5 demonstrates the effect of β -blockade on k_{SM} on one dog. In all six dogs, k_{SM} fell with β -

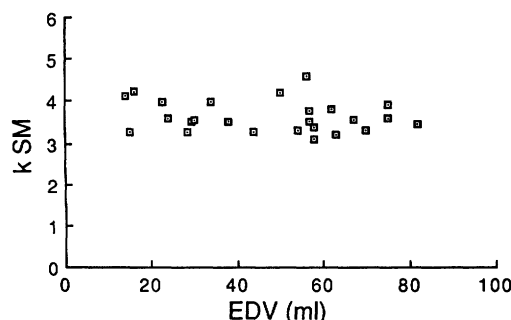


FIGURE 3. Relation between the end-systolic elastic stiffness constant of the myocardium (k_{SM}) and end-diastolic volume (EDV) in 25 β -blockaded dogs. k_{SM} was nearly constant, with the value of 3.6 ± 0.4 over a wide range of EDV.

blockade (4.3 ± 0.7 to 3.5 ± 0.3 , $p < 0.05$), correctly demonstrating decreased contractile state with a known negative inotrope. β -Blockade also decreased E_{ES} in each case from 8.5 ± 5.8 to 5.5 ± 4.4 ; however, the decrease was not statistically significant. Heart rate decreased modestly after propranolol from 131 ± 15 to 108 ± 14 beats/min ($p = 0.05$). Systolic blood pressure (105.8 ± 16.3 mm Hg) did not change after propranolol (103 ± 12.2 mm Hg). Left ventricular end-diastolic pressure (8.7 ± 2.5 mm Hg) also was unchanged after propranolol (9.0 ± 2.4 mm Hg).

Table 1 summarizes the influence of change of inotropic state on k_{SM} and E_{ES} . Both indexes demonstrated a significant decrease with isoflurane and a significant increase with dobutamine. Figure 6 demonstrates the effect of the changes in inotropic state on one dog.

Table 2 summarizes the studies to determine whether the relation was primarily linear or curvilinear over a wide range of stresses and to determine the effects of preload on the relation. Whereas a linear fit always yielded a good correlation, the correlation for a curvilinear fit was better in every case. The r value using the curvilinear fit for all 12

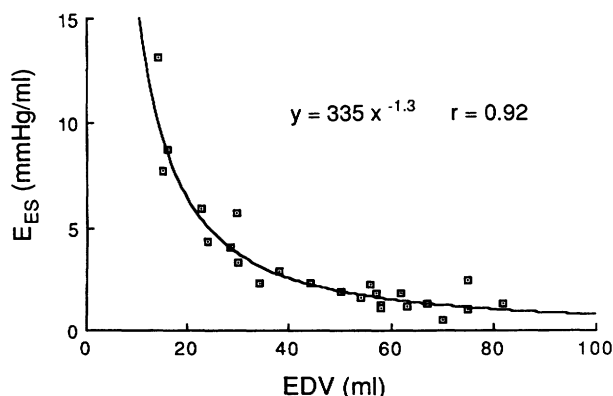


FIGURE 4. Relation between the slope (E_{ES}) of end-systolic pressure-volume relation (ESPVR) and end-diastolic volume (EDV) in all dogs during β -blockade. E_{ES} was closely related to EDV by a logarithmic function ($ESPVR = 335 \times x^{-1.3}$, $r = 0.92$).

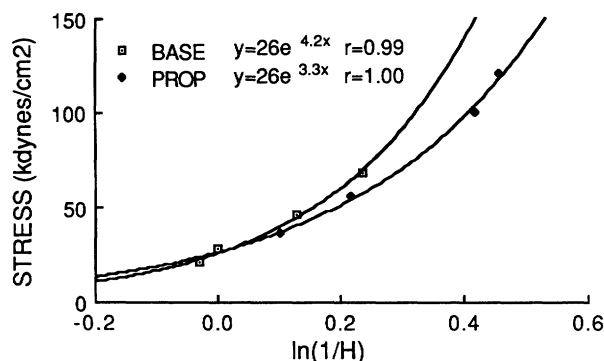


FIGURE 5. Effect of β -blockade with propranolol (PROP) on the end-systolic stiffness constant of the myocardium (k_{SM}) from a representative dog. β -Blockade decreased k_{SM} from 4.2 to 3.3. BASE, baseline without propranolol; $\ln(1/H)$, natural logarithm of the reciprocal of wall thickness.

determinations was statistically better than the linear fit. An example is shown in Figure 7. Infusion of 1 l saline increased the left ventricular end-diastolic pressure from 11.8 ± 0.9 to 24.7 ± 1.7 mm Hg ($p < 0.001$). However, there was no change in k_{SM} between these two states (k_{SM} , 3.64 ± 0.37 , baseline; 3.46 ± 0.37 , saline). The average difference between the two states was $6.4 \pm 5\%$. In 11 cases in which seven or more consecutive variably loaded beats were available for analysis, we compared k_{SM} obtained from the simple geometric Equation 14 with the more general Equation 15. No statistical difference was found. The mean k_{SM} for the simple form was 3.6 ± 0.3 versus 3.5 ± 0.5 for the more general equation.

Discussion

An important finding of this study was that k_{SM} was independent of ventricular size, whereas ESPVR was dependent on ventricular size. k_{SM} was distributed within a narrow range among β -blocked subjects. Furthermore, k_{SM} increased appropriately when inotropic state was increased and decreased appropriately when inotropic state was decreased.

Size Dependence of End-Systolic Pressure-Volume Relations

The contractile state of the myocardium is its ability to generate force. This property has been found to be prognostic of outcome in a wide range of cardiac diseases. Thus, many investigators over the past 30 years have sought to find indexes that mea-

TABLE 1. Effects of Changes in Inotropic State on End-Systolic Contractility Indexes

	Control	β -Blockade + isoflurane	Dobutamine
k_{SM}	3.7 ± 0.5	$3.1 \pm 0.3^*$	$4.8 \pm 0.8^\dagger$
E_{ES} (mm Hg/ml)	2.6 ± 1.5	$1.6 \pm 1.0^*$	$5.6 \pm 2.5^*$

Values are given as mean \pm SD. k_{SM} , end-systolic elastic stiffness constant; E_{ES} , slope of the end-systolic pressure-volume relation.

* $p < 0.05$ compared with control.

$^\dagger p < 0.01$ compared with control.

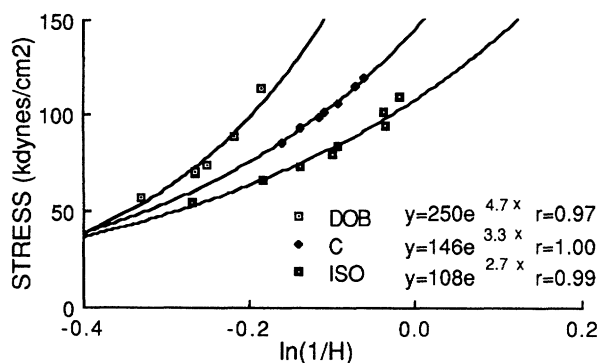


FIGURE 6. Effects of inotropic changes on the end-systolic stiffness constant of the myocardium (k_{SM}) from a representative dog. Isoflurane (ISO) decreased k_{SM} from 3.3 to 2.7 and dobutamine (DOB) increased k_{SM} to 4.7. C, control state under β -blockade; $\ln(1/H)$, natural logarithm of the reciprocal of wall thickness.

sured contractile state. The ideal contractile index should be 1) sensitive to changes in contractile state, 2) insensitive to changes in preload and afterload, and 3) independent of cardiac size. Over the past 15 years, the concept of time varying elastance and the determination of maximum elastance has undergone intensive investigation as an index of contractile function.¹⁻⁶ This concept has given way to its approximation by E_{ES} of the ESPVR based on the premise that, in the ejecting heart, maximum elastance usually occurs near or at the end of systole.^{32,33} E_{ES} is sensitive to changes in contractile state but relatively insensitive to loading conditions. Originally hypothesized to be linear,¹⁻³ the relation has more recently been found to be curvilinear,^{11,34-36} although this may not be relevant in the physiological range of pressure variation. The most serious limitations of E_{ES} , however, is its dependence on ventricular size.^{4,7,10} Systemic pressure in most mammalian systems operates within a narrow range, yet volume ranges widely according to the size of the subject. Thus, E_{ES} of the ESPVR in a normal rat with normal contractile function will be much steeper than E_{ES} in

TABLE 2. Linearity Versus Curvilinearity of Stress–Area Strain Relation

	Dog	k_{SM}	% Δ	r_e	r_L
Baseline	1	5.01		0.994	0.973
	2	4.26		0.993	0.991
	3	2.59		0.998	0.997
	4	3.15		0.999	0.993
	5	2.97		0.987	0.981
	6	3.85		0.996	0.993
Infusion	1	4.73	-5.6	0.996	0.954
	2	4.33	+1.6	0.997	0.982
	3	2.52	-2.7	0.983	0.982
	4	3.22	+2.2	0.997	0.987
	5	2.61	-12.1	0.982	0.974
	6	3.34	-13.2	0.986	0.985
	Mean	3.55	6.4	0.992	0.983*
	SD	0.81	5	0.005	0.007

k_{SM} , Myocardial stiffness constant; % Δ , percent change in k_{SM} from baseline after saline infusion; r_e , correlation coefficient of wall stress and strain [$\ln(1/H)$] using an exponential fit; r_L , correlation coefficient of wall stress and area strain using a linear fit.

* $p=0.02$ for r_e versus r_L .

a normal elephant. Less dramatic but similar changes occur among individuals of different size within the same species.⁸

Several methods of correction of E_{ES} have been proposed.⁷⁻¹² Normalizing for body weight or body surface area is probably acceptable if ventricular size within the individual remains normal.⁸ However, this method might not be able to correct for a change in ventricular size that occurs in a volume overload state because it is ventricular size, not the body surface area, that is changing. Correction of E_{ES} by end-diastolic volume also has been proposed,¹² but an increase in end-diastolic volume could be caused either by eccentric hypertrophy, by an increase in preload, or by both.³⁷ In this last instance, multiply-

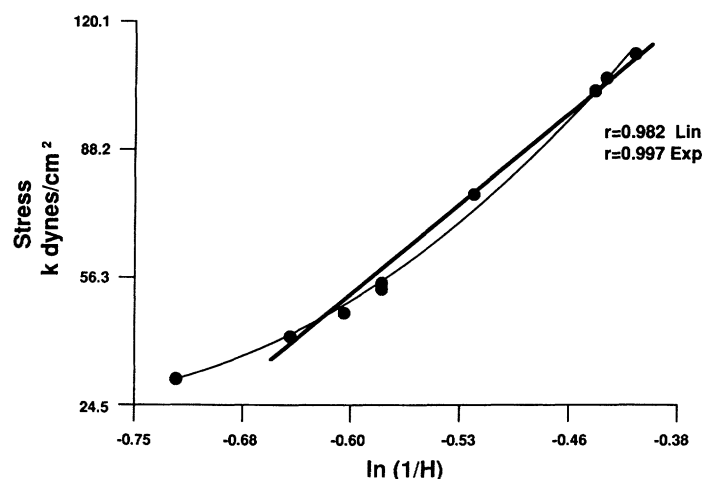


FIGURE 7. A linear (Lin) versus curvilinear (Exp) fit to the same stress-strain points from a dog receiving methoxamine. Whereas the correlation coefficient (r) is good using a linear fit, the exponential correlation coefficient is higher. $\ln(1/H)$, natural logarithm of the reciprocal of wall thickness.

ing the E_{ES} by the end-diastolic volume accounts not only for new sarcomeres laid down in series (the intended correction) but also for an increase in sarcomere stretch (yielding an overcorrection). Several authors have suggested a normalization of E_{ES} for unstressed volume,^{7,9,11} however, unstressed volume is theoretical and cannot be confirmed. Thus, ESPVR remains a useful, accurate tool to measure acute changes in contractile state within a single individual. However, it is difficult to use this method when comparing subjects of differing size to one another or when comparing subjects to themselves if eccentric cardiac hypertrophy has intervened.

The End-Systolic Stress- $\ln(1/H)$ Relation

This relation uses a principle similar to the ESPVR in examining contractile state: The stiffness of the ventricle reaches its maximum value at the end of systole in the ejecting heart. The end-systolic σ - $\ln(1/H)$ coordinates (the left upper corner of the end-systolic σ - $\ln[1/H]$ loop) obtained at various loads at a constant inotropic state produce an exponential relation, the exponent of which (k_{SM}) increases as inotropic state increases and decreases as inotropic state decreases. However, because k_{SM} is a stress-strain relation, it does not require size correction. In an elegant study, Mirsky et al¹¹ successfully applied the concept of myocardial stiffness to the end-systolic relation. Although our method also is based on myocardial stiffness, the fundamental components of calculating wall stress and strain are somewhat different. First, we used wall stress calculated as the division of isotropic wall tension by wall thickness to express the force within the ventricular wall by one simple scalar variable, whereas Mirsky et al calculated the difference between circumferential and radial stress and strain. Second, because we examined only incremental changes in stress and $\ln(1/H)$, we could use $\ln(1/H)$ instead of $\ln(H_0/H)$. Thus, we could avoid the use of unstressed wall thickness (H_0), that is, wall thickness at zero stress, which is a clinically unobtainable variable. Third, we fit the end-systolic σ - $\ln(1/H)$ relation to an exponential curve, whereas Mirsky et al extrapolated it from linear regression.

Curvilinearity and Load Independence in Stress- $\ln(1/H)$ Relation

In previous studies,^{16,17,22} the σ - $\ln(1/H)$ relation appeared linear. These studies were performed using aortic constriction to vary load. In the initial current studies, inferior vena cava balloon inflation was used to alter load at lower levels of pressure. Under these circumstances, the relation appeared curvilinear. To resolve this issue, we performed experiments in which hypertension was created to broaden the range over which the relation could be developed. These experiments demonstrated that the σ - $\ln(1/H)$ relation clearly was curvilinear. Whereas the linear fit to the data points achieved a correlation coefficient (r) greater than 0.95 in every case, also in every case, the

exponential fit achieved a higher value of r than the linear fit. These studies also demonstrated that the relation was insensitive to changes in preload. Volume expansion significantly increased left ventricular end-diastolic pressure (from which we infer increased preload) but did not significantly change k_{SM} . Furthermore, despite the change in loading conditions, k was reproducible, varying by an average of only 6.4% between determinations.

Contractility in Puppies and Adult Dogs

To maximize size variation, we studied puppies and adult dogs. The k_{SM} in puppies was similar to that of adult dogs (3.7 ± 0.4 and 3.6 ± 0.4 , respectively). Suga et al²³ studied peak isovolumic pressure-volume development in puppies aged 2–4 months and in adult dogs and found peak force-generating capacity was reduced in puppies. Unlike the relatively linear isovolumic pressure-volume relation in adult dogs, the puppy left ventricle had an upwardly convex relation that limited peak isovolumic pressure development. This difference occurred at ventricular pressures higher than 120 mm Hg. However, the isovolumic peak pressure-volume relation at pressures of 70–100 mm Hg was linear in puppies and adult dogs. Furthermore, the effects of positive and negative inotropic intervention on peak isovolumic pressure-volume relations in the puppy were similar to those in adult dogs. Because we reduced the volume during our ventriculograms, pressures generally were at a level at which the pressure-volume relation for puppies and adult dogs was linear. Thus, in the pressure range studied, our puppies and adult dogs probably had similar contractile function.

Limitations

To simplify the method to make its application practical, we made some assumptions that must be addressed. First, the end of systole was defined volumetrically as the frame when the aortic valve closed and hemodynamically as the aortic diastolic notch pressure. Suga et al¹ have indicated that the slope of instantaneous pressure-volume relation usually reaches a maximum value near the end of ejection at the uppermost left corner of the pressure-volume relation. Although these points may not always coincide with maximum stiffness, the points we used are “hard” end points that can be accurately defined and do not require matching of pressure and volume at other more arbitrary points in time. Furthermore, we assumed that myocardial mass remained constant throughout systole. We recognize that cyclic variations in coronary blood flow may alter intramyocardial blood volume such that this assumption is not completely valid^{38,39}; we could not ascertain the effects of this on k_{SM} .

Previous studies of indexes of contractile state have demonstrated dependence on alterations in vascular tone.⁴⁰ We did not test this property in our study. However, k values during methoxamine infusion, a vasoconstrictor, were similar to values

obtained without methoxamine in other dogs, suggesting that this vasoconstrictor did not greatly alter the σ -ln(1/H) relation.

In this study, we assume that the ventricle is isotropic, that is, that its elastic properties are the same in all directions. However, previous authors have demonstrated a physiological base-to-apex torsion and myocardial shear during the cardiac cycle.⁴¹⁻⁴³ In all studies, the amount of shear was small, and we have estimated that neglecting shear forces introduces approximately only a 3% error into our method.¹³ However, this error could increase in hypertrophy or ischemia, when shear forces could be greater.

We assumed an ellipsoidal model for the left ventricle but actually measured the long axis in each case. A change in shape of the ventricle toward spherical should be detected and corrected for by the area-length method and stress formula that we used.

Finally, the end-systolic σ -ln(1/H) relation was fitted to a simple exponential curve expressed as $\sigma = C e^{k \ln(1/H)}$. The fitting of end-systolic σ -ln(1/H) with $\sigma = C e^{k \ln(1/H)}$ limits the stress asymptote to zero and gives no x intercept. Theoretically, when the stress is zero, strain is zero, and the end-systolic σ -ln(1/H) curve should have an x intercept. In an excised cross-circulated heart, the lower part of end-systolic σ -ln(1/H), where pressure is close to zero, might be possible to obtain.¹⁻³ However, in an in vivo study, this is impossible, because the contractility of the left ventricle becomes depressed as coronary perfusion falls at such low pressure.^{27,38,39} The most general form of the exponential curve equation is:

$$\sigma = C' e^{k' \ln(1/H)} + B \quad (15)$$

In this equation, the asymptote is unlimited. However, the fitting of end-systolic σ -ln(1/H) to this general form is difficult in some cases when the number of data points during volume unloading is small. To test the difference between the simple exponential curve expressed as $\sigma = C e^{k \ln(1/H)}$ (Equation 14) and that obtained from Equation 15, we compared those curves in 11 cases in which seven or more points of end-systolic σ -ln(1/H) were obtained. No statistical significance was found among curves. Thus, approximation of end-systolic σ -ln(1/H) as a simple exponential equation appears valid.

In conclusion, we introduce a new approach for assessing the contractile state of the left ventricle using the relation between end-systolic stress and ln(1/H). This end-systolic relation is exponential. The exponential constant k_{SM} , which is the myocardial stiffness constant, is sensitive to changes in contractile state and is independent of ventricular size. We also have demonstrated preload independence of the relation. Thus, k_{SM} should be a useful index for comparing myocardial contractility among individuals with different ventricular size and among different pathological states in the same individual. Although its derivation is complex, the index itself is easily calculated from readily available clinical parameters.

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KEY WORDS • contractility • myocardial stiffness • ventricular function