Linearity of the Frank-Starling relationship in the intact heart: the concept of preload recruitable stroke work


ABSTRACT The Frank-Starling relationship generally has been examined with filling pressure as the index of preload, resulting in a curvilinear function that plateaus at higher filling pressures. To investigate this relationship further in the intact heart, 32 dogs were chronically instrumented with left ventricular and pleural micromanometers and with regional (10 dogs) or global (22 dogs) ultrasonic dimension transducers. Seven days after implantation, left ventricular pressure and regional or global dimensions were recorded in the conscious state. After autonomic blockade, preload was varied by vena caval occlusion. Myocardial function was assessed by calculating regional or global stroke work, and preload was measured as end-diastolic segment length or chamber volume. The relationship between stroke work and either end-diastolic segment length or chamber volume (termed the preload recruitable stroke work relationship) was highly linear in every study (mean r = .97) and could be quantified by a slope (M_w) and x-intercept (L_w). Previous nonlinear relationships between stroke work and filling pressure seemed to reflect the exponential diastolic pressure-volume curve. Over the physiologic range of systolic arterial pressures produced by infusion of nitroprusside or phenylephrine, no significant change was observed in M_w or L_w in the normal dog. Calcium infusion increased both regional and global M_w by 71 ± 19% and 65 ± 9%, respectively (p < .02), with no significant change in L_w. To normalize for ventricular geometry and heart rate, stroke work was computed from circumferential stress-strain data and converted to myocardial power output, which was then plotted against end-diastolic circumferential strain. This relationship also was highly linear, and the slope, M_{dp} (mW/cm³ of myocardium), is proposed as a potential measure of intrinsic myocardial performance independent of loading, geometry, and heart rate.


QUANTIFICATION of cardiac function has been the goal of physiologists for nearly a century, but it has been difficult if not impossible to establish practical or reliable measures of intrinsic myocardial performance in the intact heart. Some indexes, such as ventricular function curves relating stroke work to filling pressures, were nonlinear and difficult to quantify. Other parameters suffered from lack of preload or afterload independence, difficulty with numerical assessment, or problems with extensive assumptions. The end-systolic pressure-volume relationship has shown promise in the isolated heart but may be less satisfactory in the intact subject. Finally, no model of systolic function currently exists that compensates for differences in chamber size or geometry.

Thirty years ago, Sarnoff and Berglund investigated various modifications of the Frank-Starling principle and suggested that the relationship between stroke work and end-diastolic volume might be linear. Despite this early speculation, controversy arose about the characteristics of the work-dimension relationship and when further reports demonstrated significant afterload sensitivity of stroke work, investigative efforts were turned in other directions. Throughout this period, however, most physiologists...
and clinicians continued to consider cardiac function intuitively within the Frank-Starling framework, even though numerical assessment was difficult. In this context, the present study was undertaken to reexamine the Frank-Starling relationship using contemporary methodology with the goals of improving the understanding of systolic function and developing practical measures of myocardial performance.

Methods

Experimental preparation. Thirty-two dogs (18 to 30 kg) were premedicated with cefazolin (250 mg) and iron dextran (100 mg) and were anesthetized with intravenous thiamylal sodium (20 mg/kg) and succinylcholine (1 mg/kg). After endotracheal intubation, each dog was ventilated with a Bennett MA1 respirator (Puritan-Bennett, Los Angeles) and a thoracotomy was performed through the left fifth intercostal space under sterile conditions. Bipolar pacing electrodes were sutured to the left atrium, and silicone rubber pneumatic occluders were positioned around both venae cavae. A silicone rubber tube (2.6 mm id, 4.9 mm od, Dow Corning, Midland, MI) was secured in the base of the left atrial appendage for later passage of a micromanometer into the left ventricle. A similar tube with multiple side holes was positioned in the pleural space near the ventricular epicardial surface for measurement of pleural pressure.

In 10 dogs, cylindrical ultrasonic dimension transducers (1.5 mm od, No. 1-1015-5A, Vernitron, Bedford, OH) were implanted in the left ventricular midmyocardium to assess regional myocardial segment length. The transducers were placed 10 to 15 mm apart in the left ventricular minor axis circumference. Three crystals were placed in each dog, as shown in figure 1, to ensure at least one functioning crystal pair. In the remaining 22 dogs, global left ventricular dimensions were measured with epicardially placed hemispheric dimension transducers. One pair of hemispheric transducers was oriented across the minor axis diameter (figure 1), and the other was positioned in the major axis direction. In six global preparations, electromagnetic flow probes (HQ series, Howell Instruments, Camarillo, CA) were implanted on the ascending aorta. All connectors, tubes, and cables exited through the chest wall into a subcutaneous pouch dorsal to the incision. The pericardium was left widely open, and the thoracotomy was repaired in layers. Each dog was allowed to recover for 7 to 10 days before hardware was exteriorized through a small incision in the skin with 1% lidocaine local anesthesia.

Data acquisition and experimental design. One day after exteriorization, each dog was sedated with morphine (0.7 mg/kg im) and studied in the conscious state while lying quietly on its right side. The ultrasonic dimension transducers were coupled directly to a sonomicrometer constructed from the design of Rushmer et al. The sonomicrometer and amplifier system had a practical frequency response of 0 to 50 Hz with a minimum resolution of 0.08 mm and maximal electronic drift of 0.05 mm/hr.

Micromanometers (Model PC-350, Millar Instruments, Houston) were passed through the implanted tubes into the left ventricle and pleural space. The micromanometers were prewarmed in a water bath at 38°C under constant electrical excitation by a pressure amplifier (Model 8805-C, Hewlett-Packard, Waltham, MA) and were simultaneously balanced and calibrated immediately before each study. Resultant manometer drift was less than 0.5 mm Hg/hr, and the useful frequency response exceeded 10 kHz. Electromagnetic flow probes were connected to a gated sine wave flowmeter (M4001, Statham, Los Angeles) with a useful frequency response of 0 to 50 Hz. Each probe was calibrated before implantation with a gravity-fed saline system. Aortic blood flow was assumed to be zero at end-diastole.

In each dog, pharmacologic attenuation of autonomic reflexes was accomplished by intravenous administration of propranolol (1 mg/kg) and atropine (0.1 mg/kg). Autonomic blockade was considered adequate if the spontaneous heart rate changed by less than 10% during vena caval occlusion and release. Additional doses of propranolol and atropine were administered as necessary throughout the study to maintain a constant heart rate and an adequate level of autonomic attenuation. During each intervention, physiologic data were digitized during a steady-state period and also during vena caval occlusions. After control data were obtained, the preparations were paced atrially at rates of 100, 120, 140, and 160 beats/min under normal afterload conditions. Upon return to steady-state conditions, phenylephrine (0 to 1.6 μg/kg/min, 10 μg/kg maximum dose) and nitroprusside (0 to 30 μg/kg/min) were infused intravenously in random order to obtain a wide range of physiologic arterial pressures. Between drug infusions, sufficient time was allowed to permit each dog to return to control conditions. Calcium chloride (15 mg/kg) then was infused intravenously.
and vena caval occlusions were repeated. Finally, phenylephrine was infused, and the blood volume expanded with intravenous normal saline to achieve nonphysiologic left ventricular systolic pressures greater than 200 mm Hg and end-diastolic pressures greater than 30 mm Hg. Throughout the studies, data were accepted for analysis only if the spontaneous heart rate varied by less than ±10% under all conditions (indicating minimal change in autonomic balance).

At the conclusion of each study, the dog was killed, an autopsy was performed, and proper position of the transducers was confirmed. Left ventricular wall volume was measured by saline displacement after excising the atria, right ventricular free wall, aortic and mitral valves, and chordae tendineae.

**Data analysis.** All data were filtered by a 50 Hz low-pass analog filter and digitized in real time at an eight-channel sweep speed of 200 Hz by an analog-to-digital converter (Model 1012, ADAC, Woburn, MA). The conversion time per channel was 30 μsec, imposing a phase delay between channels of less than 4.5 degrees. After data collection and storage on digital magnetic tape, data analysis was performed on a microprocessor (Model PDP 11/23, DEC, Maynard, MA) with interactive programs developed in our laboratory. Left ventricular transmural pressure was calculated as the difference between left ventricular and pleural pressures. The first time derivative of left ventricular transmural pressure (dP/dt) was computed from the digital pressure waveform as a running five-point polyorthogonal transformation. In the remainder of this article, all left ventricular pressures will be presented as transmural pressures.

The cardiac cycle was defined automatically with dP/dt. Beginning ejection was placed 10 msec after peak positive dP/dt and correlated closely with initiation of aortic flow under all loading conditions. End-ejection was defined at peak negative dP/dt, agreeing well with the zero crossing of aortic flow as described by Abel.22 Diastole was assumed to begin with the first zero crossing of dP/dt after peak negative dP/dt and ended 40 msec before a positive dP/dt of greater than 500 mm Hg/sec.

Beat point definitions were checked visually on all data with a videographics display system. The requirement for redefinition was rare according to the criteria listed above.

For global data, left ventricular cavity volume (V) was calculated from epicardial major (a) and minor (b) axis diameters by representing the epicardial surface of left ventricle as an ellipsoidal shell and subtracting ventricular wall volume (Vwall):

\[ V = \pi b^2a - V_{wall} \]  

(1)

Global net stroke work (SW) was calculated as the integral of left ventricular transmural pressure (P) and cavity volume over each cardiac cycle as described by the formula:

\[ SW = \int P \cdot dV \]  

(2)

Stroke work also was calculated from aortic flow probe data by the equation:

\[ SW = SV \cdot (MEP - EDP) \]  

(3)

where stroke volume (SV) was the time integral of aortic flow over ejection and MEP and EDP were left ventricular mean ejection pressure and end-diastolic pressure. A regional stroke work analog was calculated as the integral of segment length (L) and left ventricular transmural pressure:

\[ SW = fP \cdot dL \]  

(4)

Ventricular power output (VPO) was calculated by the formula:

\[ VPO = SW \cdot \text{heart rate} \]  

(5)

Normalized minor axis circumferential stroke work was calculated as:

\[ SW = f\sigma \cdot dz \]  

(6)

and myocardial power output (MPO) was calculated as:

\[ MPO = \text{heart rate} \cdot f\sigma \cdot dz \]  

(7)

where σ was circumferential midwall equatorial wall stress, and ε was circumferential midwall equatorial strain (see Appendix). The term “myocardial power output” was selected because this derived variable described power normalized per unit myocardium. In all formulas, the kinetic component of stroke work was omitted since it has been shown to be less than 1% to 5% of total stroke work under physiologic conditions.1, 14

Linear regression analysis was performed on data from individual vena caval occlusions. Data from 5 beats before onset of occlusion to steady-state maximal vena caval occlusion were included in the analysis, unless heart rate changed by more than 10%. By linear regression analyses, data were fitted to the formulas:

\[ SW = M_w (EDV - V_w) \]  

(8)

\[ SW = M_w (EDL - L_w) \]  

(9)

\[ VPO = M_{ep} (EDV - V_p) \]  

(10)

\[ MPO = M_{ep} (EDc - \epsilon_{mp}) \]  

(11)

relating stroke work (SW), ventricular power output (VPO), and myocardial power output (MPO) to left ventricular end-diastolic volume (EDV), segmental end-diastolic length (EDL), or end-diastolic circumferential strain (EDc) with slopes Mw, Mep, and Mmp and x-intercepts Vw, Lw, Vp, and \epsilon_{mp}. Physiologic variables were compared by Student’s paired or unpaired t test. The effect of calcium on regression slopes and x-intercepts was tested after expressing means as percent of control. Afterload dependence of mean data was evaluated by the nonparametric Wilcoxon ranked sign test. The effect of heart rate on stroke work and ventricular power output was examined by one-way analysis of covariance with heart rate as the covariate. Unless otherwise stated, all values are expressed as mean ± SEM.

**Results**

Typical digital data from regional and global studies are shown in figure 2. With infusion of phenylephrine or nitroprusside, a range of mean ejection pressures was achieved from 90 to 200 mm Hg, along with appropriate changes in left ventricular dimensions and end-diastolic pressures. When stroke work was plotted as a function of end-diastolic volume or segment length for global or regional studies, respectively, linear relationships consistently resulted as shown in figure 3 and table 1 (mean r = .97). This extreme linearity was always observed, even beyond end-diastolic pressures of 30 mm Hg. Relationships obtained during vena caval occlusion and release did not differ significantly if autonomic attenuation was adequate and if vena caval occlusion duration was less than 30 sec. The mean slopes of the work-dimension relationships (Mw) were 123 ± 31 and 69 ± 8 erg · cm⁻³ · 10³ for regional and global studies, respectively (table 1). Although zero stroke work seldom was achieved at maximal vena caval occlusion, the minimum work value generally was small, averaging 18 ± 10% (mean ± SD) of control stroke work. Thus calculation of the x-
Since error.

The x-intercepts of PRSW relationships were designated L_w for regional studies and V_w for global studies. Values of L_w and V_w did not differ significantly from the unstressed diastolic segment length (L_o) or volume (V_o) measured during maximal caval occlusion at 0 mm Hg ventricular diastolic transmural pressure (p > .3). This apparent identity between x-intercepts (L_w and V_w) and unstressed cardiac dimensions (L_o and V_o) was also noted after infusions of calcium, phenylephrine, and nitroprusside.

The effects of varying arterial blood pressure on PRSW relationships are shown in figure 4 for representative regional and global studies. At a given end-diastolic dimension, phenylephrine increased mean ejection pressure, decreased ejection shortening or stroke volume, and had no significant effect on stroke work, which was approximately the product of mean ejection pressure and ejection shortening or stroke volume. Similarly, nitroprusside decreased mean ejection pressure, increased ejection shortening or stroke volume, and also had a negligible effect on stroke work. As shown in figure 5 and table 2, mean data from eight regional studies and eight global studies demonstrated no significant influence of mean ejection pressure (over the range from 100 to 200 mm Hg) on either the slope (M_w) or x-intercept of PRSW relationships (p > .2). Consequently, physiologic alterations in mean ejection pressure produced little change in stroke work at a constant end-diastolic dimension (p > .14). Few valid data were obtainable in the conscious dog outside the range of mean ejection pressures from 100 to 200 mm Hg; beyond these limits, the spontaneous heart rate consistently changed by greater than 10%, suggesting reflex overriding of autonomic attenuation.

The results of increasing inotropic state with calcium infusion are illustrated in table 1. For regional and global studies, the increase in M_w during calcium infusion averaged 71 ± 19% and 65 ± 9%, respectively (p < .02). In regional studies, calcium infusion produced a statistically but probably not physiologically significant 2 ± 1% decrease in the x-intercept, L_w (p < .05), whereas no significant change was observed in V_w for global studies (p > .5).

Typical regional and global PRSW relationships before and during calcium infusion are shown in figure 6. When stroke work was plotted as a function of end-diastolic pressure (left panels), nonlinear ventricular function curves were obtained. However, when the same data were plotted with end-diastolic segment length or volume as the index of preload, linear PRSW relationships resulted (middle panels), which responded to infusion of calcium simply by a change in slope. Differences between linear and nonlinear work curves could be explained by the exponential relationship between diastolic pressure and dimension (right panels).
As reported previously,28 passive diastolic pressure-dimension curves were not affected by infusion of calcium in the normal heart.

To validate calculation of global cardiac work from ventricular volume, stroke work computed from aortic flow (equation 3) was compared with stroke work calculated from chamber dimensions (equation 2). The mean correlation coefficient obtained in six dogs was consistently high (mean $r = .96$, $p < .001$), but as seen in figure 7, stroke work calculated from aortic flow was less at higher values of stroke work than that calculated from integration of pressure-volume loops (average slope $= 0.82 \pm 0.02$; average x-intercept $= -417 \pm 111 \text{ erg} \cdot \text{cm}^3$). The right panel of figure 7 suggests that the difference between the two stroke work calculations resulted from overestimation by equation 3 of the amount of diastolic work done on the left ventricle. This difference, however, was generally small, especially at normal filling pressures.

To normalize for differences in ventricular geometry, stroke work was calculated as the area enclosed by the circumferential stress-strain loop depicted in figure 8, A. Normalized circumferential work calculated by equation 6 again was a linear function of dimensional preload as shown for one study in figure 8, B, and for all studies in table 3. The x-intercepts of these relationships were not significantly different from zero ($p > .4$) and differed from zero at all only because strain was normalized to dimensions at 0 mm Hg diastolic transmural pressure instead of values at zero stroke work (see Appendix). The mean slope of the circumferential work vs strain relationship was $113 \pm 24 \text{ erg} \cdot \text{cm}^3 \cdot \text{mm}^{-1}$ (mean $\pm$ SD). Relationship slopes did not correlate appreciably with heart size ($V_{\text{wah}}$) over the range studied ($r = .1$, $p > .6$).

To evaluate alterations in heart rate, stroke work and ventricular power output were plotted as functions of end-diastolic volume in six dogs. Again, data represent vena caval occlusions at constant paced heart rates. As demonstrated in figure 9, A, and table 4, the slope of the linear relationship between stroke work and end-diastolic volume did not change significantly with heart rate over the range of 100 to 160 beats/min ($p > .5$). However, the slope ($M_{\text{vp}}$) of the ventricular power output vs end-diastolic volume relationship increased proportionally with heart rate (figure 9, B and C). The linear equation relating the ratio between two values of $M_{\text{vp}}$ at different heart rates (HR) to the change in heart rate was:

$$\frac{M_{\text{vp}_1}}{M_{\text{vp}_2}} = 0.0092 (\text{HR}_1 - \text{HR}_2) + 1.015$$  \hspace{1cm} (12)

Finally, the concepts of power output and geometry normalization were combined in figure 10 and table 3 by relating normalized circumferential stroke work per unit time (myocardial power output from equation 7) to end-diastolic circumferential strain. As stated previously, all data were acquired during transient vena caval occlusion at a constant heart rate. Again, highly linear relationships were obtained (mean $r = .95$) with x-intercepts not significantly different from zero ($p > .4$). The mean relationship slope ($M_{\text{vp}}$) was $10.4 \pm 1.9 \text{ mW/cm}^3$ of myocardum (mean $\pm$ SD).

**Discussion**

The ability to quantify systolic myocardial performance is essential for a thorough understanding of cardi-
ac pathophysiology and is especially crucial in evaluating processes that alter the contractile state. By most definitions, an index of contractility or myocardial inotropic must assess the capacity of the heart to perform work and must also be independent of preload and afterload. Although physiologists have devised many measures of contractile performance over the last century, most indexes have suffered from impracticality or significant load dependence.5

As early as 1882, Fick30 and Blix30 initiated quantitative studies of skeletal muscle physiology by demonstrating a direct relationship between fiber length and contractile function. Frank31 in 1895 and Starling32 in 1914 described similar relationships for cardiac muscle. In Starling’s words, “The mechanical energy set free on passage from the resting to the contracted state depends on the . . . length of the muscle fibers.”33 In 1954 Sarnoff and Berglund3 showed that myocardial contractile performance could be described reliably by nonlinear ventricular function curves relating ventricular stroke work to filling pressure. However, nonlinear curves had the disadvantage of being difficult to quantify, and the use of pressure as the index of preload introduced susceptibility to such extraneous influences as pericardial pressure34, 35 and septal shifting.36 Given these difficulties, Sarnoff speculated that “a plot of work against volume (or fiber length) would be closer to a straight line.”31 Unfortunately, technology at that time did not allow accurate measurement of dynamic cardiac dimensions or volume.

Ultimately, dimensional analysis was applied, but controversy arose regarding fundamental aspects of the work-dimension (PRSW) relationship. As usual, most discrepancies probably represented methodologic differences between studies. For example, experiments demonstrating nonlinearity of PRSW relationships usually used less reliable techniques of measuring cardiac dimensions such as mercury-in-Silastic gauges,13, 14, 16 whereas findings from other investigations using sonomicrometry17, 34, 37 or volumetric methods9-11, 14 suggested PRSW curves might be relatively linear. Techniques of altering cardiac preload also have varied, and volume infusion,1, 14, 16, 34, 38-40 decreased venous return,17, 25, 41 and vasopressor bolus38, 42 each have been used in intact animals and man. The comparability of vasopressor

<table>
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<tr>
<th>TABLE 1</th>
<th>PRSW relationship slopes and x-intercepts under control conditions and during calcium infusion</th>
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r = linear correlation coefficients; n = sample size.

aExpressed as millimeters for the regional study and as milliliters for the global study.

bP < .05 vs control by paired t test.
FIGURE 4. Typical effects of afterload variation by phenylephrine and nitroprusside in one regional study (left panels) and one global study (right panels). Mean ejection pressure (top panels), segment ejection shortening or stroke volume (middle panels), and stroke work (bottom panels) are plotted vs end-diastolic segment length or volume.

bolus to other means of varying preload was questionable because of the extreme afterload changes and confounding alterations in autonomic reflexes and myocardial blood flow. Finally, techniques of varying systemic arterial resistance, such as arteriovenous fistulas, rapid aortic occlusion and infusion of norepinephrine, phentolamine, or angiotensin probably were not comparable because of β-adrenergic effects in the absence of autonomic blockade or because of potential differences in cardiac responses to transient vs steady-state loading alterations. Therefore, it is difficult to make strict comparisons between studies or conclusions drawn from diverse protocols. At present, vena caval occlusion seems to be the best method for varying preload, and steady-state infusion of phenylephrine in the presence of autonomic blockade must be considered the standard of reference for varying afterload in the intact.
certainly, net stroke work should be a more appropriate measure of systolic performance in the intact heart.

Although several investigators supported the finding of minimal afterload sensitivity of stroke work,9, 38, 44 others showed evidence that stroke work fell either with increasing or decreasing ventricular afterload.1, 10, 20, 21, 47 These differences may relate to a more prominent afterload dependence of isolated10, 11, 21 or open-chest anesthetized preparations.1, 19, 47 These ventricles have depressed myocardial function as compared with the ventricles of conscious dogs, and afterload sensitivity may be greater because of a more prominent impedance matching phenomenon.42 Even in the normal conscious dog, however, the obvious certainty that external stroke work must be zero at both zero and infinite afterload implies a plateau in the work-afterload relationship to explain the apparent small effects of arterial load on stroke work over the physiologic range of arterial pressures (figure 5). If relationships for dysfunctional ventricles differ from those observed in the normal dog, application of similar analyses to pathophysiologic situations may require modification of the PRSW model to take into account afterload dependence. Nonetheless, the results of several experimental studies of isolated papillary muscles,2 isolated hearts,10, 21 and anesthetized areflexic dogs47 suggest a plateau-like relationship and partially support the findings of the present study.

The geometric models used to calculate ventricular volume and stroke work with sonomicrometry have been validated elsewhere.25, 26 In the present experiments, stroke work computed from cardiac dimensions correlated well with stroke work based on aortic flow (figure 7), except at higher filling pressures for reasons stated previously. Finally, the results of previous studies16 support the calculation of regional stroke work from equation 3, where ventricular transmural pressure was substituted for myocardial fiber force (F) in the exact equation:

$$SW = F \cdot dL$$

(13)

The substitution of pressure for force probably was valid in short-term experiments, since linear relationships between myocardial force and ventricular pressure have been demonstrated previously43 and since segmental stroke work has been shown to relate linearly to global stroke work over wide ranges of heart rate, preload, afterload, and inotropic state.16

Based on simple geometric principles, ventricular volume should depend on the cube of fiber length. It
TABLE 2
PRSW relationship slopes and x-intercepts for control conditions and after infusion of phenylephrine and nitroprusside

<table>
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<tr>
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<th>Control Slope (erg·cm⁻³·10³)</th>
<th>Control X-intercept</th>
<th>Phenylephrine Slope (erg·cm⁻³·10³)</th>
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<td>1.4</td>
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</table>

Missing data were excluded for heart rate change greater than ±10%. Average mean ejection pressures were 131 ± 4, 175 ± 6, and 106 ± 3 mm Hg for control, phenylephrine, and nitroprusside, respectively. The effects of phenylephrine and nitroprusside on observed slopes and intercepts were not significant by Wilcoxon ranked sign test.

*Expressed as millimeters for the regional study and as milliliters for the global study.

was therefore surprising that the PRSW relationship was linear, with both ventricular volume and myocardial segment length used as the index of preload. However, several investigators have demonstrated experimentally that left ventricular minor axis diameter and segment length are related linearly to ventricular volume. This quasilinear length-volume relationship probably resulted from the fact that ventricular shortening and deformation occurred predominantly in the minor axis direction during ejection and filling. Although relationships would vary with long-term changes in regional geometry caused by ischemia or hypertrophy, volume-length, work-length, or work-diameter curves in short-term experiments were always linear regardless of orientation of segmental or diameter transducers. This finding justifies a simplified dimensional approach to future assessment of short-term directional changes in myocardial function, in which only one dimension and left ventricular pressure need to be measured.

The effects of autonomic reflexes in this study were minimized during vena caval occlusion by blocking the autonomic nervous system pharmacologically and by excluding data associated with a change in heart rate of more than 10%. The constancy of the linear PRSW relationship during both vena caval occlusion and release suggested that autonomic reflexes were suppressed adequately. Moreover, significant autonomic alterations during phenylephrine or nitroprusside infusion were unlikely, given the constancy of spontaneous heart rate and the demonstrated ability of autonomic blockade to minimize direct α-adrenergic effects of phenylephrine. Finally, as demonstrated by Berne and our group, myocardial ischemia induced by a 30 sec vena caval occlusion is minimal as a result of effective coronary autoregulation and decreasing oxygen demand.

The results of this study have important implications regarding the practical assessment of cardiac performance. First, the observed linearity of the PRSW curve confirms the speculations of Starling and Sarnoff and indicates that the curvilinear relationship between stroke work and filling pressure resulted from the exponential nature of the diastolic pressure-volume-
Avoidance of filling pressure as the index of preload should minimize the problematic influences of pericardial pressure, septal shifting, or respiratory variations in intrapleural pressure. Linearity of the PRSW relationship also allows quantification of cardiac performance by a simple slope and x-intercept. Utility for assessing inotropic state is suggested by the sensitivity of the slope (Mw) to calcium infusion while the x-intercept (Vw) remained constant. The small but statistically significant decline in regional x-intercept with infusion of calcium probably represented systematic artifacts in extrapolation to the x-axis. In fact, no significant changes in Vw or diastolic V₀ were observed for global data under any of the conditions tested; this finding suggested that both Vw and V₀ reflected the unstressed diastolic volume, which was a passive variable and was independent of short-term changes in systolic myocardial performance. The constancy of Vw...
with changes in afterload, inotropic state, and heart rate implies that once \( V_w \) is determined (perhaps by extrapolation), only one point on the linear PRSW relationship need be measured to define \( M_w \) and directional changes in inotropic state on a beat-to-beat basis. Therefore, application of the PRSW concept to experimental and clinical problems should be facilitated. The variability among dogs in PRSW relationship slopes (standard deviations of 31%, 24%, and 19% of mean for \( M_w \), \( M_p \), and \( M_{opt} \), respectively) was moderate and may well reflect biological variability in myocardial performance between animals or some type of experimental variability.

Practicality of the PRSW relationship was emphasized further by the finding that ventricular volume, minor axis diameter, or segment length could be used to assess preload. Since preload reduction by vena caval occlusion transiently decreased work nearly to zero, the x-intercept could be determined with relative ease and minimal extrapolation. Since the x-intercept (\( L_w \) or \( V_w \)) and the unstressed diastolic dimension (\( L_o \) or \( V_o \)) were equivalent, the necessary information was available from measurement of either variable. The apparent identity of \( V_w \) to \( V_o \) had the corollary that stroke work should be zero at 0 mm Hg end-diastolic pressure. Although a 0 mm Hg early diastolic transmural pressure was obtainable in all studies, 0 mm Hg end-diastolic pressure and thus zero stroke work were seldom achieved by vena caval occlusion, probably because of continued minimal venous return from the heart.

FIGURE 8. Circumferential stress-strain loops in one study (A) with the resultant relationship between end-diastolic circumferential strain and normalized circumferential stroke work (B) calculated as the area enclosed by each circumferential stress-strain loop.

### TABLE 3

<table>
<thead>
<tr>
<th>Study</th>
<th>( V_{wall} ) (ml)</th>
<th>Slope (erg cm(^{-3}) 10(^3))</th>
<th>X-intercept</th>
<th>r</th>
<th>n</th>
<th>( \text{Slope} ) (mW cm(^{-3}))</th>
<th>X-intercept</th>
<th>r</th>
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\( V_{wall} \) = left ventricular wall volume; \( r \) = correlation coefficient; \( n \) = sample size.
FIGURE 9. Effects in one study of heart rate on the relationships between stroke work and end-diastolic volume (A) and ventricular power output and end-diastolic volume (B). C, Effects of heart rate on mean stroke work–EDV relationship slopes (Mw) and ventricular power output–EDV relationship slopes (Mwp) for six studies. (Statistical analysis presented in table 4.) D, Relationship between Mwp ratio and heart rate change (Δf). Data were acquired during transient vena caval occlusion at each constant, paced heart rate.

azygous vein and coronary sinus. However, the minor differences observed in Vw and V0 did not seem practically significant. Interestingly, ventricular volume never decreased below V0, even with maximal preload reduction and inotropic stimulation. This observation may have ultrastructural explanations at the level of the sarcomere.

To qualify as an index of myocardial contractility or inotropism by traditional definitions,52 a parameter must be responsive to changes in inotropic state and also must be independent of preload and afterload. The PRSW relationship was indeed preload independent because it was defined by varying diastolic fiber length. Moreover, since data from this study demonstrated afterload insensitivity over the physiologic range, the PRSW relationship approximated a true index of inotropic state in the normal dog heart. Theoretically, however, stroke work cannot be afterload independent over the entire range of arterial resistance.2,21,47 In fact, to date no potential “index of contractility” has been demonstrated to be independent of both preload and afterload over a wide range in the intact subject. The effective nonexistence of any true contractile index, along with the practical reality that only a finite range of loading conditions are ever achievable, severely undermines the concept of contractility.

Instead of contractile indexes, it may be far more reasonable to discuss indexes of ventricular function that do exist and are measurable. As defined by Sonnenblick and Strobeck,53 an index of ventricular performance relates an ejection parameter such as work or power to preload and is not necessarily afterload independent. In fact, load sensitivity may vary with the
TABLE 4
Effects of heart rate on stroke work or ventricular power output vs end-diastolic volume relationships

<table>
<thead>
<tr>
<th>Stroke work</th>
<th>Heart rate (beats/min)</th>
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<tr>
<td>study</td>
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<tr>
<td></td>
<td>( M_w ) (erg cm(^{-3}) 10(^{-3}) )</td>
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<tr>
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<table>
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<tbody>
<tr>
<td>study</td>
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<td></td>
<td>( M_{vp} ) (mW cm(^{-3}) )</td>
</tr>
<tr>
<td>27</td>
<td>14</td>
</tr>
<tr>
<td>28</td>
<td>11</td>
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<tr>
<td>31</td>
<td>9</td>
</tr>
<tr>
<td>32</td>
<td>13</td>
</tr>
<tr>
<td>Mean</td>
<td>11(^{a})</td>
</tr>
<tr>
<td>SEM</td>
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</tbody>
</table>

\( M_w \) = stroke work (SW) vs EDV slope; \( M_{vp} \) = ventricular power output (VPO) vs EDV slope; \( V_w \) = SW vs EDV x-intercept; \( V_p \) = VPO vs EDV x-intercept.

\(^{a}\)The mean \( M_{vp} \) changed significantly with increasing heart rate (\( p < .05 \)).

FIGURE 10. Typical linear relationship between myocardial power output and end-diastolic circumferential strain with intrinsic myocardial function presented as \( M_{np} \). Data points represent successive cardiac cycles during transient vena caval occlusion, during which the spontaneous heart rate changed by less than 10%.

state of myocardial function and may be more pronounced in severely depressed ventricles. Utilization of the PRSW relationship may allow better conceptualization of afterload sensitivity, which itself may be an important aspect of cardiac physiology. Future ventricular performance indexes might be considerably improved by replacing two-dimensional curves with three-dimensional relationships such as work-preload-afterload\(^{57}\) or force-length-velocity surfaces.\(^{54}\) Another approach would be to relate PRSW slope (\( M_w, M_{vp}, \) or \( M_{np} \)) to arterial load in a two-dimensional analysis. Achievement of true afterload independence by incorporating the variable of arterial resistance (as outlined by Sagawa\(^{43}\) for the ventricle and by Sonnenblick\(^{54}\) for isolated muscle) might for the first time produce measurable "indexes of contractility."

In addition to being load insensitive, the ideal descriptor of myocardial performance should be independent of cardiac geometry. Over the narrow range examined in this study, \( M_w \) did not vary appreciably with cardiac size or segment length, but this is unlikely to be true when markedly dilated or hypertrophied
ventricles are considered. Theoretically, the normalized circumferential work vs strain relationship (figure 8 and table 3) should be independent of ventricular geometry, since the two variables of this relationship, circumferential stress and strain, take into account chamber characteristics. Further examination of geometric dependence over wider ranges of chamber size and myocardial function is needed, such as during growth, hypertrophy, and chamber dilatation. Should geometric independence be verified, the normalized PRSW relationship could permit reliable assessment of functional alterations at the myofibrillar level.

Any useful descriptor of myocardial performance also should respond appropriately to changes in heart rate. The rate independence of $M_w$ demonstrated in this study is consistent with data from Suga et al.\textsuperscript{55} in the isolated heart. It must be cautioned, however, that stroke work responses to steady-state alterations in heart rate may not be comparable with the results of transient frequency perturbations, in which stroke work could be quite sensitive to heart rate. The slope of the ventricular power output vs end-diastolic volume relationship, $M_{dp}$ increased linearly with increasing heart rate (table 4). Indeed, the slope of equation 12 ($9.2 \times 10^{-3}$ relating steady-state $M_{dp}$ ratio to heart rate change correlated well with the transient force-frequency slope (dP/dt ratio/ΔHR) of $8.6 \times 10^{-3}$ measured by Arentzen et al.,\textsuperscript{56} who used postextrasystolic potentiation. Such close agreement suggests that changes in intrinsic myocardial function caused by steady-state and transient alterations in contraction frequency may have similar biochemical mechanisms.

Linearity of the PRSW relationship supports the conviction of Starling that the length-dependence phenomenon reflects a basic property of cardiac muscle at the cellular level.\textsuperscript{32} Although Starling’s knowledge of cellular mechanics was limited, subsequent studies have confirmed Starling’s speculations. Crozatier et al.\textsuperscript{57} and Yoran et al.\textsuperscript{58} found that sarcomere lengths in the intact heart seldom exceeded the range of 1.8 to 2.2 μm, where developed sarcomere force has been shown to be relatively independent of sarcomere length.\textsuperscript{59} With active force (F) constant, sarcomere stroke work (SW) or the integral of the length (L)-force product would be proportional to both the initial length (EDL) as Starling predicted and to the final length (ESL): \[ SW = \int F \cdot dL = F \int dL = F(EDL - ESL) \] (14)

Factors such as transmural fiber recruitment\textsuperscript{58} and recruitment of unaligned fibers,\textsuperscript{60} which make developed sarcomere force insensitive to cardiac preload or initial fiber length, also may contribute to PRSW relationship linearity in the intact ventricle. The work of Sonnenblick and Skelton\textsuperscript{61} supports linearity of the work-length relationship at the cellular level, and, as Starling speculated, length dependence of myocardial function may reflect fundamental mechanical and energetic cellular processes.

Potential applications of the PRSW concept to the field of myocardial energetics are suggested by the work of Suga et al.\textsuperscript{55} In the isolated heart, Suga et al. demonstrated that myocardial oxygen consumption correlated linearly with the systolic pressure-volume area bounded by the end-diastolic pressure-volume curve and the linear end-systolic pressure-volume relationship, including the systolic portion of the pressure-volume loop. Since pressure-volume area and myocardial energy production both are approximate direct functions of end-diastolic volume, the findings of Suga et al. may reflect a basic relationship between myocardial oxygen consumption or energy utilization and mechanical energy output. Further investigation of this topic within the PRSW framework, taking into account efficiency of energy transfer, could simplify our understanding of myocardial energetics in normal and diseased hearts.

In conclusion, the relationship between stroke work and end-diastolic dimensions in the normal conscious dog was independent of preload, seemed insensitive to physiologic changes in afterload, and was responsive to alterations in inotropic state. With appropriate normalization, the relationship potentially becomes independent of cardiac geometry and heart rate, and systolic myocardial performance may be assessed by one number, $M_{wp}$, expressed in milliwatts per cubic centimeter of myocardium. Further investigation of these concepts is needed in the diseased heart, but PRSW and other similarly derived relationships potentially could provide insights into cardiac pathophysiology in a variety of experimental and clinical settings.

Appendix

Circumferential wall stress and strain were calculated by modeling the left ventricle as a prolate ellipsoid with internal volume (V)\textsuperscript{22}:
\[ V = \frac{\pi}{6} (b - 2h)^2 (a - 1.1h) \] (15)
where $a =$ left ventricular external major axis diameter, $b =$ left ventricular external minor axis diameter, and $h =$ left ventricular equatorial wall thickness.

Combining equation 15 with equation 1,
\[ V = \frac{\pi}{6} b^2 a - V_{\text{wall}} \] (1)

wall thickness ($h$) may be calculated as a root of the cubic equation:
\[ h^3 - \left[ \frac{b + 1.1a}{1.1} \right] h^2 + \left[ \frac{ab}{1.1} \right] h - \left[ \frac{6V_{\text{wall}}}{4.4\pi} \right] = 0 \] (16)
Circumferential wall stress ($\sigma$) was computed with calculated wall thickness in the formula\(^6\):

$$\sigma = \frac{P (b - h)}{2h} \left[1 - \frac{(b - h)^3}{2} \left(\frac{a - .55h}{2} \right)^2 \right]$$  \hspace{1cm} (17)

where P = left ventricular transmural pressure. Circumferential Lagrangian strain ($\varepsilon$) was calculated from the formulas:

$$C = \pi (b - h)$$ \hspace{1cm} (18)

$$\varepsilon = \frac{C - C_0}{C_0}$$ \hspace{1cm} (19)

where $C$ is left ventricular midwall equatorial circumference and $C_0$ is left ventricular midwall equatorial circumference at maximal vena caval occlusion and 0 mm Hg diastolic transmural pressure.

We gratefully acknowledge the technical aid of Ron Johnson and Ruth Rodgers, the engineering support of Steve Avert, and the secretarial assistance of Sandra Justice and Paula Poe.

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Circulation. 1985;71:994-1009
doi: 10.1161/01.CIR.71.5.994
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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