Comparison of Measures of Left Ventricular Contractile Performance Derived From Pressure-Volume Loops in Conscious Dogs

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Three measures of left ventricular (LV) performance derived from pressure (P)-volume (V) loops have been proposed: the end-systolic P-V (P_Es-V_Es), the stroke work-end-diastolic V (SW-V_ED) relation, and maximum dP/dt-V_ED (dP/dtmax-V_ED) relation. We evaluated the variability of repeated determinations, and inotropic and load sensitivity of these relations in conscious dogs. LVV was determined from three orthogonal LV diameters measured by sonomicrometry. Three to six sets of variably loaded P-V loops were generated by transient caval occlusions before and again after increasing inotropic state by infusing dobutamine (6±1 μg/kg/min, mean±SD) and after increasing P_ES by 49±17 mm Hg with phenylephrine following autonomic blockade. The slope (MSW) of the SW-V_ED relation was the least variable at constant inotropic state (coefficient of variation, 4±3%) compared with the slope (E_ES) of the P_ES-V_ES relation (8±3%) or the slope (dE/dtmax) of the dP/dtmax-V_ED relation (11±6%, p<0.05). The extrapolated volume-axis intercept of the SW-V_ED relation was much less variable than the intercepts of the P_ES-V_ES or dP/dtmax-V_ED relations. MSW, E_ES, and dE/dtmax all increased (p<0.05) in response to dobutamine. The extrapolated volume-axis intercepts of the P_ES-V_ES and dP/dtmax-V_ED relations increased with dobutamine, whereas the volume intercept of the SW-V_ED relation was unchanged. MSW had the smallest increase in response to dobutamine (124±22% of control) compared to E_ES (178±67% of control) and dE/dtmax (211±68% of control, p<0.05). The position of the P_ES-V_ES relation, quantified as the V_ES at P_ES=100 (V_100), showed less variability (2±1%) than the slope of the P_ES-V_ES relation (8±3%, p<0.05). V_100 decreased from 30.8±17.4 to 26.7±13.7 ml during dobutamine (p<0.05). After phenylephrine, E_ES, MSW, and dE/dtmax decreased by less than 10% (p=NS). The P_ES-V_ES relation shifted to the left with this increased afterload and V_100 decreased by 3.2±1.5 ml (p<0.05), whereas the position of the SW-V_ED and dP/dtmax-V_ED relations were relatively unchanged. We conclude that the SW-V_ED relation that integrates data from the entire cardiac cycle is the most stable but also the least sensitive to changes in inotropic state, whereas the dP/dtmax-V_ED relation is the most sensitive but also most variable measure of the contractile state. In contrast to the P_ES-V_ES and dP/dtmax-V_ED relations, the volume-axis intercept of the SW-V_ED relation can be reproducibly determined in conscious animals and is not altered by enhanced contractile state. (Circulation 1989;80:1378–1387)

The evaluation of left ventricular (LV) performance is an important problem in clinical practice and physiologic investigation. Conventional measures of LV performance, such as ejection fraction, and maximum rate of change of LV pressure (dP/dt_max) are influenced not only by the contractile state but also by loading conditions. To help overcome these limitations, LV performance has been analyzed in the pressure-volume (P-V) plane. Initially, most attention was focused on the LV end-systolic pressure (P_ES)-volume (V_ES) relation. The slope of a linear approximation of this relation (E_ES) responds to the contractile state and is relatively insensitive to loading conditions. However, recent observations suggest that the P_ES-V_ES relation may be quite variable in conscious ani-
mals,8,9 that a linear approximation may not always be appropriate,10,11 and that arterial loading conditions may shift the relation.2,6,8,12–14

Recently, two other measures of LV performance derived from variably loaded LV P-V loops have been proposed2,15: linear relations between dP/dt_{max} and the end-diastolic volume (V_{ED}), and between LV stroke work (SW) and V_{ED}. Both the dP/dt_{max}V_{ED} and P_{ES}-V_{ES} relations can be derived from the time-varying elastance model of the LV.2 The SW-V_{ED} relation is a modification of the traditional Frank-Starling cardiac function curve in which LV end-diastolic pressure is replaced by V_{ED}.15 This substitution linearizes the relation. The slopes of the dP/dt_{max}V_{ED} and SW-V_{ED} relations have been reported to respond to changes in the contractile state but not load alterations.2,15 No study has directly compared these three relations derived from P-V analysis of the LV of the conscious animals. Accordingly, the purpose of this study was to simultaneously assess the P_{ES}-V_{ES}, dP/dt_{max}V_{ED}, and SW-V_{ED} relations in conscious dogs, comparing their variability and response to alterations in the contractile state and load. We hypothesized that because the SW-V_{ED} relation integrates data from the entire cardiac cycle, it would show little variability over repeated determinations, but that it may be less sensitive to changes in the contractile state than the dP/dt_{max}V_{ED} relation because dP/dt_{max} reflects the velocity of contraction.16 Furthermore, we hypothesized that although the dP/dt_{max}V_{ED} relation is very sensitive to altered contractile state,2,17 it may be less stable and more variable than the SW-V_{ED} or P_{ES}-V_{ES} relations.

**Methods**

**Instrumentation**

Fourteen healthy, adult mongrel dogs (weight, 30±3 kg) were instrumented with a previously described technique.18,19 A left lateral thoracotomy was performed under anesthesia with halothane (1–2%) after induction with xylazine (1 mg/kg) and sodium thiopental (6 mg/kg). The pericardium was opened widely. A micromanometer pressure transducer (P6.5, Konigsberg Instruments, Pasadena, California) and a polyvinyl catheter for transducer calibration (i.d., 1.1 mm) were inserted through the LV apex. Three pairs of ultrasonic crystals (5 MHz) were implanted in the endocardium of the LV to measure the anteroposterior, septalateral, and base-apex (long-axis) dimensions. Hydraulic occluder cuffs were placed around the inferior and superior venae cavae.

**Data Collection**

Studies were performed after full recovery from the thoracotomy (10 days to 2 weeks) with the animals awake and lying quietly on their right sides in a sling. The LV catheter was connected to a pressure transducer (Statham P23DB) calibrated with a mercury manometer. The signal from the micromanometer was adjusted to match that of the catheter. The transit time of 5-MHz sound between the crystal pairs was determined and converted to distance, assuming a constant velocity of sound in blood of 1.55 m/msec, using a sonomicrometer (mode 120, Triton Technology, San Diego, California). The analog signals were recorded on an eight-channel oscillograph (MT 8500, Astro-Med West Warwick, Rhode Island) and digitized with a 12-bit analog-to-digital converter (Data Translation Devices, Marlboro, Massachusetts) at 200 Hz.

**Production of Variably Loaded Pressure-Volume Loops**

Data were recorded during a steady-state control period to obtain baseline values. A set of variably loaded P-V loops was then generated by the sudden transient occlusion of the cavae. This caused a progressive fall in LV end-systolic pressure, volume, and dP/dt_{max} over a 12-second recording period (Figure 1). Immediately after the recording period, the caval occlusion was released. After all parameters returned to their baseline level, the caval occlusions were repeated until three to six (mean±SD, 4±1) sets of P-V loops were produced.

**Altered Contractile State**

The effect of the increased contractile state was assessed in 11 dogs. Sufficient atropine (0–2 mg i.v.) was administered to abolish the marked sinus arrhythmia frequently present in conscious dogs. Steady-state data were collected, then three to six sets of variably loaded P-V loops were generated by transient caval occlusion. Dobutamine was infused at a rate (6±1 µg/kg/min) sufficient to increase dP/dt_{max} by more than 500 mm Hg/sec. After repeating the steady-state recordings, three to six sets of variably loaded P-V loops were generated.

**Effect of Altered Load**

The effect of increased arterial load was assessed in nine dogs. Autonomic blockade was produced with hexamethonium, 5 mg/kg i.v., and atropine, 0.1 mg/kg i.v., to prevent reflex changes in the contractile state. Steady-state measurements and three to six sets of variably loaded P-V loops were obtained. Then phenylephrine (0.1–0.2 mg i.v.) was administered to increase LV systolic pressure by about 50 mm Hg (49±17 mm Hg). Approximately 5–10 minutes after beginning the phenylephrine infusion, three to six sets of variably loaded P-V loops were obtained.

**Data Analysis**

The stored digitized data were analyzed by computer algorithm. Baseline hemodynamic values in each dog were obtained by averaging the data obtained during the 12-second steady-state recording periods. End systole was defined as the upper left-hand corner of the LV P-V loop defined using
the iterative technique described by Kono et al.\textsuperscript{20} End diastole was defined as the relative minima following the a wave of the high-fidelity LV pressure tracing. The LV volume was calculated as a modified general ellipsoid using the equation:

\[ V_{LV} = \frac{(\pi/6)}{D_{Ap}D_{Sl}D_{La}} \]

where \( D_{Ap} \) is the anteroposterior LV dimension, \( D_{Sl} \) is the septolateral LV dimension, and \( D_{La} \) is the long-axis LV dimension. We have previously evaluated this method of volume calculation,\textsuperscript{5,18,21-23} and it is similar to that used and validated by others,\textsuperscript{24} except that we determined endocardial dimensions directly, making unnecessary the subtraction of LV wall thickness or volume. This method of volume calculation gives a consistent measure of LV volume \((r>0.97, \text{ SEE}<2 \text{ ml})\) despite changes in LV loading conditions, chamber configuration, and inotropic state. SW was calculated by point-by-point integration of the LV P-V loop for each beat, as described by Glower et al.\textsuperscript{15} The time-derivative of LV pressure \((dP/dt)\) was calculated using the five-point LaGrange method.\textsuperscript{25}

Only caval occlusions that produced a fall in LV systolic pressure of at least 30 mm Hg were analyzed. Premature beats and the subsequent beat were excluded from analysis. Beats occurring after the heart rate had increased by more than 10% of the initial value were also excluded. The LV \( P_{ES} - V_{ES} \) data during the fall of LV pressure produced by each caval occlusion were fit using the least-squares technique to:

\[ P_{ES} = E_{ES}(V_{ES} - V_0) \]

where \( E_{ES} \) is the slope of the linear \( P_{ES} - V_{ES} \) relation, representing the LV end-systolic elastance, and \( V_0 \) is the intercept with the volume axis. To quantify the position of the \( P_{ES} - V_{ES} \) relation in the operating range, the volume \((V_{100})\) associated with a \( P_{ES} \) of 100 was calculated as:

\[ V_{100} = V_0 + 100/E_{ES}. \]

The \( dP/dt_{max} \) and \( SW - V_{ED} \) relations were quantified by fitting the data from the same beats from each caval occlusion used to evaluate the \( P_{ES} - V_{ES} \) relation to:

\[ dP/dt_{max} = dE/dt_{max} (V_{ED} - V_0,dP/dt) \]

and

\[ SW = M_{SW} (V_{ED} - V_{0,SW}). \]

The slope of the \( dP/dt_{max} - V_{ED} \) relation, \( dE/dt_{max} \), theoretically represents the maximum rate of change of LV elastance.\textsuperscript{2,16,27}

The positions of the \( dP/dt_{max} - V_{ED} \) and \( SW - V_{ED} \) relations in the operating range were calculated by determining \( V_{ED} \) associated with \( dP/dt \) of 2,000 mm Hg/sec and SW of 2,000 mm Hgml:

\[ V_{2,000,dP/dt} = V_0,dP/dt + 2,000/(dE/dt_{max}) \]

\[ V_{2,000,SW} = V_{0,SW} + 2,000/M_{SW}. \]

Curvilinearity of the relations were evaluated as previously described by fitting the data to quadratic equations.\textsuperscript{10,26} A zero coefficient of the squared term indicates no deviation from linearity, whereas a negative coefficient indicates the relation is concave toward the x axis and a positive coefficient indicates it is convex toward the x axis.

\textit{Postmortem Studies}

At the conclusion of the experiments, the animals were killed with an overdose of barbiturates, and
the hearts were examined to confirm the proper positioning of the instrumentation.

Statistical Methods

The slopes, volume-axis intercepts, and positions of each of the three relations for each condition were evaluated as the mean values of three to six caval occlusions performed under each condition. The variation at the constant contractile state was assessed using the coefficient of variation calculated as SD/mean expressed as a percent.

Results are summarized as the mean±1 SD, and the level of significance was p<0.05. Multiple comparisons were performed by analysis of variance or Friedman’s test. Intergroup comparisons were performed by paired t tests or Wilcoxon tests with an appropriate correction for the performance of multiple comparisons using the Bonferroni inequality.27

Results

An analog recording following caval occlusion is shown in Figure 1, and the resulting set of variably loaded P-V loops is shown in Figure 2A. The $P_{ES}$-$V_{ES}$, $dP/dt_{max}$-$V_{ED}$, and $SW$-$V_{ED}$ relations from this and two additional caval occlusions are shown in Figures 2B–2D. At the constant contractile state, with repeated determinations, $M_{SW}$ was less variable (4±3%) than $E_{ES}$ (8±3%, p<0.05) or $dE/dt_{max}$ (11±6%, p<0.05) (Table 1). There were no consistent differences in these values between the first and last caval occlusion. The position of the relations, quantified as $V_{100}$, $V_{2,000,SW}$, and $V_{2,000,dP/dt_{max}}$, were more reproducible than the slopes. Caval occlusion produced a larger range of values of SW than $P_{ES}$ or $dP/dt_{max}$; thus, less extrapolation of the SW-$V_{ED}$ relation was required to obtain the zero-pressure volume-axis intercept ($V_{0,SW}$). There was large variability in the extrapolated volume intercepts of the $P_{ES}$-$V_{ES}$ (15±20%) and $dP/dt_{max}$-$V_{ED}$ (24±55%) relations, but the volume intercept of the SW-$V_{ED}$ relation varied by only 2±1% between caval occlusions. The volume intercepts of the $dP/dt_{max}$-$V_{ED}$ and $P_{ES}$-$V_{ES}$ relations were not significantly dif-
fenter, but the volume intercept of the SW-VED relation was 12.1±7.4 ml greater than the volume intercept of the P_ES-VES relation (p<0.05) and 16.6±11.3 ml greater than the volume intercept of the dP/dt_max-VES relation (p<0.05). The steady-state hemodynamic variables are shown in Tables 2 and 3. During the 12-second control period, dP/dt_max was only slightly more variable (1.4%±0.7%) than SW (1.1±0.5%, p=NS).

The slopes of the three relations, dE/dt_max, E_ES, and M_SW, all significantly (p<0.05) increased in response to dobutamine (Table 2 and Figure 3). dE/dt_max showed the greatest increase (211±68% of control) in response to the augmented contractile state with dobutamine, whereas M_SW showed the smallest increase (124±22% of control). All three relations were shifted toward the left in the operating range with the enhanced contractile state, manifest by significant increases in V_{100}, V_{2,000,dpdr}, and V_{2,000,sw} (Table 4). The shift of the dP/dt_max-VES relation was significantly greater than the shift of the SW-VED or P_ES-VES relations. Thus, the dP/dt_max-VES relation showed the greatest response to dobutamine, both in terms of the increased slope and the leftward shift. The extrapolated volume-axis intercepts of the P_ES-VES and dP/dt_max-VES relations increased with dobutamine, whereas volume intercept of the SW-VED relation remained constant.

Although all three relations were well described by straight lines with correlation coefficients typically greater than 0.96, the P_ES-VES relation was slightly but consistently concave toward the volume axis. This was apparent as a negative coefficient of the V_ES^2 term in the quadratic fit of the P_ES-VES relation. This coefficient was statistically less than zero, and similar during control (−0.6±0.6 mm Hg/ml) and after dobutamine (−0.6±0.7 mm Hg/ml), but was somewhat less negative after phenylephrine (−0.26±0.22 mm Hg/ml) (Table 5) and was still significantly less than zero. Similarly, the dP/dt_max-VES relation also tended to be concave toward the volume axis. The coefficients of the V_ES^2 term were significantly different from zero both during control (−3.0±3.9 mm Hg/sec·ml^2) and after dobutamine (−3.9±4.5) and following increased afterload produced by phenylephrine (−1.86±2.20). In contrast, the SW-VED relation showed no consistent deviation from linearity. The coefficients of SW^2 terms were not different from zero, being 0.8±1.8 mm Hg during control, 1.0±1.8 after dobutamine, and 0.4±1.0 following phenylephrine (p=NS).

Increased afterload tended to decrease the slope of all three relations, although none of these changes reached statistical significance (Table 4 and Figure 4). The positions of the dP/dt_max-VED and SW-VED relations were not altered by increased afterload (V_{2,000,dpdr} and V_{2,000,sw} were similar). However, V_{100}}
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PES-VES Relation  

dP/dtmax-VED Relation  

SW-VED Relation  

FIGURE 3. One set of variably-loaded pressure-volume loops before (control) and after contractile state was increased with dobutamine as shown in Panel A. PES-VES (B), dP/dtmax-VED (C), and SW-VED (D) points derived from these loops and two additional caval occlusions are shown.

dP/dtmax-VED Relation  

Dobutamine  
Control  

Pressure (mmHg)  

20 30 40 50 60 70 80 90 100 110 120 130 140 150 160  

Volume (ml)  

0 20 40 60 80 100 120 140 160  

PES (mmHg)  

0 100 200 300 400 500 600 700 800 900 1000  

VES (ml)  

0 100 200 300 400 500 600 700 800 900  

( df/dt) (mmHg/ml)  

0 1000 2000 3000 4000  

VED (ml)  

0 100 200 300 400 500 600 700 800  

Dobutamine  
Control  

Table 4. Effect of Dobutamine on PES-VES, dP/dtmax-VED, and SW-VED Relations

<table>
<thead>
<tr>
<th></th>
<th>PES-VES Relation</th>
<th>dP/dtmax-VED Relation</th>
<th>SW-VED Relation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>E SES V SES V IDES</td>
<td>dE/dtmax V 0,dP/dt V 2,000,dP/dt</td>
<td>M SW V 0,SW V 2,000,SW</td>
</tr>
<tr>
<td>Control</td>
<td>7.4±3.2 13.5±9.8 30.8±17.4</td>
<td>93.2±49.1 8.14±16.9 40.0±28.1</td>
<td>75.9±30.5 27.6±15.6 58.7±20.0</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>13.3±9.0* 15.8±10.6* 26.7±13.7*</td>
<td>188±107* 12.1±15.7* 27.4±16.6*</td>
<td>95.9±48.5* 25.9±15.1 53.8±16.4*</td>
</tr>
</tbody>
</table>

E SES, slope of PES-VES relation; V SES, volume axis intercept of PES-VES relation; V IDES associated with PES of 100 mm Hg; dP/dtmax, maximum rate of change of LVP; V ED, end-diastolic volume; dE/dtmax, slope of dP/dtmax-VED relation; V 0,dP/dt, V ED associated with dP/dtmax of 2,000 mm Hg/sec; SW, LV stroke work; M SW, slope of SW-VED relation; V 0,SW, volume intercept of SW-VED relation; V 2,000,SW, V ED associated with SW of 2,000 ml · mm Hg.

*p<0.05 compared with control.

decreased when afterload was increased, reflecting a leftward shift of the PES-VES relation.

Discussion

In this study, we simultaneously assessed three relations that can be derived from variably loaded P-V loops: 1) the PES-VES, 2) the dP/dtmax-VED, and 3) the SW-VED relations. An optimal measure of the LV contractile state should be reproducible, sensitive to the altered contractile state, and insensitive to marked alterations in loading conditions. We evaluated all three relations by these standards. The slopes of all three increased in response to the augmented contractile state, and all three relations shifted toward the left in the range from which data were collected. The slope of the dP/dtmax-VED relation, dE/dtmax, was the most sensitive to the altered contractile state but also displayed the greatest
TABLE 5. Effect of Phenylephrine on the $P_{ES}$-$V_{ES}$, $dP/dt_{max}$-$V_{ED}$, and SW-$V_{ED}$ Relations

<table>
<thead>
<tr>
<th></th>
<th>$P_{ES}$-$V_{ES}$ Relation</th>
<th>$dP/dt_{max}$-$V_{ED}$ Relation</th>
<th>SW-$V_{ED}$ Relation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$E_{ES}$</td>
<td>$V_{ES}$</td>
<td>$V_{DE,ES}$</td>
</tr>
<tr>
<td>Control</td>
<td>7.1±2.7</td>
<td>21.0±7.3</td>
<td>36.7±13.9</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>6.7±2.6</td>
<td>17.8±5.48</td>
<td>34.5±13.2*</td>
</tr>
</tbody>
</table>

$P_{ES}$, left ventricular end-systolic pressure; $V_{ES}$, end-systolic volume; $E_{ES}$, slope of $P_{ES}$-$V_{ES}$ relation; $V_{0,ES}$, volume axis intercept of $P_{ES}$-$V_{ES}$ relation; $V_{DE,ES}$, associated with $P_{ES}$ of 100 mm Hg; $dP/dt_{max}$, maximum rate of change of LVP; $V_{ED}$, end-diastolic volume; $dE/dt_{max}$, slope of $dP/dt_{max}$-$V_{ED}$ relation; $V_{0,DF,ES}$, volume intercept of $dP/dt_{max}$-$V_{ED}$ relation; $V_{2,000,DF,ES}$, $V_{ED}$ associated with $dP/dt_{max}$ of 2,000 mm Hg/sec; SW, LV stroke work; $M_{SW}$, slope of SW-$V_{ED}$ relation; $V_{0,SW}$, volume intercept of SW-$V_{ED}$ relation; $V_{1,000,SW}$, $V_{ED}$ associated with SW of 2,000 m ･ mm Hg.

* $p<0.05$ vs. control.

variability between determinations. In contrast, the SW-$V_{ED}$ was the most reproducible but also the least sensitive to changes in contractile state. The slopes of all three changed by less than 10% in response to a marked increase in afterload. Thus, all three relations provide useful measures of LV contractile performance.

The SW-$V_{ED}$ relation integrates data obtained throughout the cardiac cycle, thus, potentially damping out noise and beat-to-beat variations. Following caval occlusion, both determinants of SW, LV pressure, and stroke volume, fall. Thus, as shown in Figures 2–4, a larger range of SW is generated than $P_{ES}$ or $dP/dt_{max}$. In addition, the SW-$V_{ED}$ relation was the only relation that displayed no statistically significant deviation from linearity. These factors contribute to the marked stability and reproducibility of this relation. The SW-$V_{ED}$ relation depends on the position of both the end-systolic and diastolic pressure-volume relations. Because the diastolic pressure-volume relation is not altered in response to the enhanced contractile state, the

![FIGURE 4. In format similar to Figure 3, pressure-volume loops are shown in Panel A before and after infusing phenylephrine to increase arterial pressure. $P_{ES}$-$V_{ES}$ (Panel B), $dP/dt_{max}$-$V_{ED}$ (Panel C), and SW-$V_{ED}$ (Panel D) relations determined from loops in Panel A and two additional caval occlusions performed both before (control) and after infusing phenylephrine are shown.](image-url)
SW-VED relation does not move as much as the P_{ES-VES} relation in response to dobutamine.

In contrast to the V_{ES-SW} relation, which integrates data obtained throughout the cardiac cycle, the dP/dt_{max}-VED relation is derived from the period of isovolumetric contraction, when the LV is undergoing a rapid transition from a passive diastolic to an active systolic state. In addition, differentiation increases the magnitude of any noise in the LV pressure signal. Although at steady state, dP/dt_{max} does not significantly vary more from beat to beat than SW, it appears that dP/dt_{max} may be subject to greater potential beat-to-beat variation following caval occlusion. Furthermore, because the range of dP/dt_{max} produced following caval occlusions is less than the range of SW, the dP/dt_{max}-VED relation cannot be as accurately defined as the SW-VED relation. Although the dP/dt_{max}-VED relation was well approximated by a straight line, it is somewhat concave toward the volume axis. Thus, linear approximations of this relation over different ranges may also produce variations in the calculated slope. These factors are reflected in our observation that the slope of the dP/dt_{max}-VED relation is subject to almost an 11% variation between repeated determinations. This variability is somewhat counterbalanced by the increased slope sensitivity of the dP/dt_{max}-VED relation to an altered contractile state. It should be recognized that inotropic interventions such as digitalis that increase E_{ES} without changing the speed of LV contraction may not increase the slope of the dP/dt_{max}-VED relation more than E_{ES}.^17

The P_{ES-VES} relation uses data obtained at a single time in the cardiac cycle, end systole, when the state of the LV is not rapidly changing. However, at end systole, the potentially varying effects of the time course of ejection and contraction may tend to cancel. Therefore, it is not surprising that the stability of repeat determinations of the P_{ES-VES} relation is intermediate between the SW-VED and dP/dt_{max}-VED relations. Our observation of an 8% variation in repeated determinations of E_{ES} is similar to that reported by Lee et al.\(^{30}\) In contrast to observations by Crottogini et al,\(^{9}\) we found that E_{ES} responds to alterations in the contractile state.

The variability of repeated determinations of the three relations should be considered when interpreting changes resulting from an intervention. Although small changes (especially of the dP/dt_{max}-VED relation) may well be due to spontaneous variability, averaging repeated determinations, as used in this study, provides a method of improving the precision with which the parameters are defined. Moreover, the position of the relations, in the middle of the range from which the data are collected,\(^{8}\) shows less variation than the slopes, and is less dependent on the choice of the model (linear or quadratic) used to fit the data. In this study, we quantified these positions by determining the V_{ES} associated with P_{ES} of 100 mm Hg, the V_{ED} associated with SW of 2,000 mm Hg, and dP/dt_{max} of 2,000 mm Hg/sec. All three parameters decrease in response to the augmented contractile state, as the relations are shifted toward the left. The accuracy with which the position of the relations in the physiologic range can be determined and the consistent shift of the relations with inotropic stimulation make the positions of these relations ideal measures of pump function. Thus, it is important to assess the positions of the relations and not just the slopes.\(^{5}\)

We also investigated the response of these relations to a marked increase in afterload (i.e., P_{ES} increased by about 50 mm Hg). The slopes did not change by more than 10%. Although all three decreased, only the change in the slope of the dP/dt_{max}-VED relation approached statistical significance. These changes, although relatively small, may reflect an underlying curvilinearity in the relations, in which the slopes decrease at the higher ranges.\(^{2,5,10,11,26,31}\) The position of the dP/dt_{max}-VED relation and the SW-VED relation did not consistently shift with the increase in arterial load, but the P_{ES-VES} relation shifted to the left. This shift of the P_{ES-VES} relation is consistent with previous studies using other methods of producing arterial vasoconstriction in intact animals,\(^{2,6,12}\) open-chest preparations,\(^{14}\) and isolated hearts.\(^{13}\) The lack of shift of the dP/dt_{max}-VED and SW-VED relations with arterial loading is also consistent with previous reports in intact animals.\(^{2,15}\) In contrast, Baan et al\(^{14}\) found that arterial constriction shifted both the P_{ES-VES} and dP/dt_{max}-VED relations. These differing results may be due to differences in the loading protocols used in these two studies.

The leftward shift of the P_{ES-VES} relation with phenylephrine indicates an improvement of pump function with arterial loading because each end-systolic pressure is associated with a smaller end-systolic volume.\(^{5}\) This suggests that afterload and the contractile function may be interrelated and not independent determinants of LV performance.\(^{14}\) However, neither SW-VED nor dP/dt_{max}-VED relations were consistently shifted after phenylephrine. Thus, it is possible that the contractile state was not enhanced by phenylephrine. More marked increases in arterial load must influence the SW-VED relation because an isovolumic beat produces zero SW. One can speculate that the shift of the P_{ES-VES} relation with vasoconstriction may result from length-dependent activation\(^{32}\) because the LV operates at higher volumes after arterial loading. If length-dependent activation was the only mechanism, both the dP/dt_{max}-VED and P_{ES-VES} relations should be shifted toward the left. However, the dP/dt_{max}-VED and SW-VED relations were not shifted. Because the stroke volume is reduced in the highly afterloaded beats, there may be less shortening deactivation.\(^{33}\) dP/dt_{max} occurs prior to aortic valve opening, therefore, shortening deactivation should not influence the dP/dt_{max}-VED relation. The lack of shift of the dP/dt_{max}-VED relation with phenylephrine suggests that shortening deactivation may have a role in
producing the leftward shift of the $P_{ES}-V_{ES}$ relation with afterloading.

There has been interest in obtaining the volume-axis intercept of the relations. Because zero pressure, $dP/dt_{max}$, and SW cannot be obtained in an intact animal, determination of the volume-axis intercept requires extrapolation outside of the range from which data are obtained. Because SW is the product of systolic pressure and stroke volume, both of which are reduced by caval occlusion, it falls to a greater degree than $P_{ES}$ or $dP/dt_{max}$.20 Thus, as shown in Figures 2–4, less extrapolation is required to obtain the volume-axis intercept of the $SW-VED$ relation than the intercepts of the $P_{ES}-V_{ES}$ or $dP/dt_{max}-V_{ED}$ relations. This explains the much lower variability of the volume-axis intercept of the $SW-VED$ relation than the intercepts of the $P_{ES}-V_{ES}$ or $dP/dt_{max}-V_{ED}$ relations. With the enhanced contractile state, the volume intercepts of the $P_{ES}-V_{ES}$ and $dP/dt_{max}-V_{ED}$ relations increased, whereas the volume intercept of the $SW-VED$ relation remained constant. The shift of the volume-axis intercept of the $P_{ES}-V_{ES}$ relation with dobutamine may result from contractile-induced changes in the curvilinearity of the relation.10,11 The small variability in the volume intercept of the $SW-VED$ relation and its constancy despite changes in arterial load and the contractile state suggests that the volume intercept of this relation can be determined once, and then used in combination with a single measurement of SW and $V_{ED}$ to define the $SW-VED$ relation.15

Because their volume intercepts are so variable, this cannot be done with the $P_{ES}-V_{ES}$ or $dP/dt_{max}-V_{ED}$ relations.

Modeling the LV as a time-varying elastance suggests that the volume intercepts of the $P_{ES}-V_{ES}$ and $dP/dt_{max}-V_{ED}$ relations should be equal.17,27 Furthermore, the volume intercept of the $SW-VED$ relation should occur at the intersection of the $P_{ES}-V_{ES}$ and end-diastolic P-V relations. In isolated hearts where it can be directly measured, this intersection occurs at a volume slightly less than the volume intercept of the $P_{ES}-V_{ES}$ relation.24 As predicted, we found that the volume intercept of the $P_{ES}-V_{ES}$ and $dP/dt_{max}-V_{ED}$ relations were approximately equal. However, there is much scatter in our data, probably resulting from the large degree of extrapolation required to determine these values in conscious animals. In contrast to the theoretical prediction, we found that the volume intercept of the $SW-VED$ relation was consistently greater than the other volume intercepts. Although relatively linear in the range from which data is collected following a caval occlusion, the $P_{ES}-V_{ES}$ relation, when assessed over a wide range, is concave downward.10,11,26 Even in the range of data points generated by caval occlusions, we observed slight but consistent curvilinearity of both the $P_{ES}-V_{ES}$ and $dP/dt_{max}-V_{ED}$ relations. If quadratic fits are used instead of linear approximations, the extrapolated values for the volume intercept of the $P_{ES}-V_{ES}$ and $dP/dt_{max}-V_{ED}$ relations would be larger.26 These values would be closer to the volume-axis intercept of the $SW-VED$ relation, which is obtained with much less extrapolation. Thus, the difference in the volume-axis intercepts may be due to linear extrapolation of curvilinear $P_{ES}-V_{ES}$ and $dP/dt_{max}-V_{ED}$ relations. The underlying curvilinearity of the $P_{ES}-V_{ES}$ and $dP/dt_{max}-V_{ED}$ relations may also produce variation of the slope of linear approximations of these relations, if they are assessed over different ranges.

We evaluated the relations derived from variably loaded P-V loops in conscious animals. The $SW-VED$ relation, which integrates data obtained throughout the cardiac cycle, is the most stable but also the least sensitive to alterations in the contractile state. It has the widest range of values following caval occlusion, shows no deviation from linearity, and is the only relation with a reproducible volume-axis intercept that is not altered by enhanced contractile state or arterial vasoconstriction. Thus, it has advantages over the other relations to serially evaluate LV performance. It also has an advantage over the other relations, if the volume-axis intercept cannot be repeatedly determined, or if P-V loops are only available over a limited range. The $dP/dt_{max}-V_{ED}$ relation is the least reproducible but most sensitive to changes in the contractile state. Thus, it may be of greatest value in excluding small changes in the contractile state. Using data obtained from caval occlusions, the positions of these three relations in the physiologic range respond consistently to inotropic stimulation and can be determined more reproducibly than their slopes. Therefore, it is important to assess the positions of the relations and not merely their slopes. Because arterial vasoconstriction shifts the $P_{ES}-V_{ES}$ relation toward the left, the position of this relation should not be used in situations in which arterial properties are markedly altered. Because the $P_{ES}-V_{ES}$ $dP/dt_{max}-V_{ED}$ and $SW-VED$ relations have somewhat different characteristics, in many situations they can provide complementary means of evaluating LV performance from variably loaded P-V loops.

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