LABORATORY INVESTIGATION
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Comparative influence of load versus inotropic states on indexes of ventricular contractility: experimental and theoretical analysis based on pressure-volume relationships

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ABSTRACT We examined the quantitative influence of carefully controlled alterations in end-diastolic volume and afterload resistance on multiple simultaneously determined ejection and isovolumetric phase indexes of left ventricular contractile function in 23 isolated supported canine ventricles. The influence of load change on each index was compared with its sensitivity to inotropic stimulation, and this sensitivity was in turn contrasted to the response of the end-systolic pressure-volume relationship (ESPVR). Experimental data demonstrated various degrees of load sensitivity among the indexes, with a generally curvilinear relationship between load and index response for both preload and afterload alterations. The curvilinear nature of these relationships meant that over a select range of loading, many indexes demonstrated relative load independence. They also often displayed greater sensitivity to inotropic change than the ESPVR, and both factors help explain their enduring clinical utility. To further explore the influence of load and contractile state on several of the indexes, we developed a theoretical analysis, using variables common to pressure-volume relationships, in which these dependencies could be derived. The theoretical models fit very well with the experimental data, and reaffirmed the frequently curvilinear nature of the relationships. We conclude that while many clinical indexes of ventricular contractile function show significant load dependence, the information they provide can be reasonably interpreted within defined ranges of load and inotropic alteration. Any advantage of the ESPVR will derive not from the magnitude of its response to inotropic change, which is smaller than most other indexes, but from its relative insensitivity to load alteration over a wider range of load.


A WIDE VARIETY of isovolumetric and ejection phase indexes have been developed to characterize left ventricular contractile state.1-6 While each index was initially believed to have a particular theoretical or empirical advantage, many of these indexes have also been found to be influenced by alterations in loading conditions.7-11 Ejection phase indexes such as ejection fraction, systolic ejection rate, or velocity of circumferential fractional shortening, must display some afterload dependence, since they reduce to zero at infinite afterload (isovolumetric contraction) independent of contractile state. Isovolumetric phase indexes such as maximal rate of pressure rise (dP/dt_max) tend to be more preload dependent.4, 7, 10 Despite this potential lack of specificity as measures of ventricular contractile state, several indexes have proven to be clinically useful. There has even been a recent resurgence of interest in several of these measures with the advent of high-fidelity echo-Doppler cardiography. Yet there has been little quantitative assessment of load dependence over multiple carefully controlled altered loads, which would help clarify the precise range in which these indexes are most useful.

The end-systolic pressure-volume relationship (ESPVR) has been used more recently as a relatively load independent and sensitive measure of ventricular contractile state.12-16 Yet few direct comparisons of the

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sensitivity of ESPV to an alteration in inotropic state with that of other contractile indexes have been made. In one recent study in vivo, 17 dP/dtmax, despite a potential influence from preload change, was found to be as good as, if not better than, end-systolic elastance (Ees) at discerning inotropic change.

An accurate comparison of the ESPV with other contractile indexes and quantification of load sensitivities demands a preparation in which loading conditions can be precisely varied without altering the intrinsic contractile state (via changes in coronary perfusion or reflex activation). Many investigations of ventricular pressure-volume relationships have achieved this by use of an isolated, cross-perfused ejecting canine heart preparation. With this model, loading variables, coronary perfusion, and contractile state can be independently controlled.

In the present study we examined several commonly used ejection and isovolumetric phase indexes of contractile function in the isolated canine ventricle. The influence of precise alterations in preload volume and afterload resistance was determined and contrasted to the sensitivity of each index to inotropic change. In addition, we derived theoretical relationships between several indexes and variables describing preload (end-diastolic volume, Ved) afterload resistance (systemic vascular elastance), and contractile state (Ees), and compared these model predictions with the experimental data.

Methods

Surgical preparation. The isolated, supported canine ventricle preparation has been fully described previously. 18, 19 Briefly, a pair of mongrel dogs was anesthetized with sodium pentobarbital (30 mg/kg iv). The femoral arteries and veins of one dog (support dog) were cannulated and connected to a perfusion system. Coronary venous blood was returned to the femoral vein of the support dog. The perfusion system was primed with 1 liter of 50% dextran in saline, which was mixed with the blood of the support animal.

The chest of the second dog (donor) was opened and the left subclavian artery was cannulated with the arterial perfusion line (from the support dog). The right atrium was cannulated and connected to the femoral vein cannula of the support dog. The brachiocephalic artery was cannulated to monitor coronary perfusion pressure. Flow of filtered, warmed (37°C), and oxygenated blood to the isolated heart was servocontrolled (Harvard Pump Model 1215) to maintain mean perfusion pressure at 80 mm Hg in the aortic root. Once the heart was cross-perfused, the azygos vein, superior and inferior venae cavae, descending aorta, and lung hili were ligated, and the entire heart was removed from the donor dog thoracic cavity.

The heart was suspended over a collecting funnel and both ventricles and the coronary sinus were vented to air. The left atrium was opened and the cordae tendineae were detached from the mitral valve leaflets. A metal ring that served to attach the isolated heart to a servopump apparatus was sutured into the mitral valve ring. The heart was then positioned so that a water-filled latex balloon was inside the left ventricular cavity, with the mitral ring firmly fixed to the servopump.

Servopump hardware. Details of the design and performance of the volume servopump system have been previously reported. 19 Briefly, a linear motor (Linco Electronics, Model 411) controlled a piston position of a cylinder pump (Bellofram SS4-F-0M). A latex balloon was secured to a tube connected to the fluid port of the Bellofram cylinder. The cylinder, the connecting tube, and the balloon were all filled with water. A linear displacement transducer (Trans-Tek model 244-000) sensed the position of the piston, producing a signal proportional to the balloon volume. The signal was used in a negative feedback loop for comparison with a volume-command signal (see below) that represented the desired instantaneous volume. The error signal resulting from this comparison was supplied to a power amplifier (Crown DC500), which in turn drove the linear motor.

Impedance loading system. The ventricular volume command signal for the volume control servosystem was generated by the interaction between instantaneous pressure in the real ventricle and a hybrid computer that simulated arterial input impedance. 18 The left ventricular pressure measured by a micro-manometer-tipped catheter (Millar PC350) placed inside the balloon served as the input to the analog computer (Comdyne Analog Signal Processor model 808) that was programmed to solve differential equations for both the ventricular preloading and afterloading circuit.

The ventricular afterload system was a three-element Windkessel model of the aortic hydraulic input impedance. 18 Flow began when ventricular pressure exceeded that in the simulated artery. The computer calculated ventricular outflow by dividing the pressure difference between the measured left ventricular pressure and aortic pressure by the characteristic impedance. Both the filling and ejecting flow signals were continuously integrated by the analog computer and the algebraic sum of this integral and the previous ventricular volume was used as the command signal for the volume servopump. The normal value 18 for the characteristic impedance was set to 0.2 mm Hg sec/ml, the peripheral resistance (R) value to 3.0 mm Hg sec/ml, and the vascular compliance value to 0.4 ml/mm Hg.

Protocol. Two types of loading change were examined, preload change with constant afterload (figure 1, A), and afterload resistance change with fixed preload (figure 1, B). At each load, the ventricle was allowed to establish a steady state (20 to 30 sec) before data were recorded. To test the stability of contractility under a given condition, we returned to the initial conditions after obtaining the three sets of pressure-volume data, and only when the difference in the end-systolic pressures (Pes) between the first loop and the test loop at the same preload was less than 10% of the initial Pes did we accept the data. Data were rejected in less than 10% of cases and in these instances the reason for unstable contractile state was usually obvious (change in the support dog condition, equipment malfunction, etc.). The two loading sequences were as follows.

Preload change, constant afterload. We obtained pressure-volume data at four different preloads (Ved), maintaining the variables of the afterload impedance system at control values (see above). The preloads were selected so that with control afterload settings the highest preload would produce a peak systolic pressure of 100 to 120 mm Hg, and the lowest preload a peak pressure of approximately 50 to 60 mm Hg.

Afterload change, constant preload volume. Pressure-volume data were obtained at four different afterload resistance (R = 8.0, 4.0, 2.0, and 1.0 mm Hg sec/ml) with the preload (Ved) held constant. Ved was selected so that at the highest value of R, the peak systolic left ventricular pressure was 100 to 120 mm Hg.
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**FIGURE 1.** Loading sequences used to assess preload and afterload sensitivity of contractility indexes. A. Preload alteration at four levels of VED, with constant afterload impedance. B. Afterload alteration at four levels of peripheral resistance, with fixed VED, compliance, and characteristic impedance.

**Data analysis.** The data were processed with use of a 16-bit minicomputer (Data General S/130). The pressure and volume data were smoothed with a three-point, nonweighted moving average, and the indexes were calculated on the smoothed data. The following variables were used in index calculations.

**End-diastolic pressure (Ped).** End-diastole was determined at the point of onset of mechanical systole. Rather than use a dP/dt threshold, we used dE/dt, where elastance (E) was calculated by the pressure-volume ratio. The time of maximal rate of rise of the pressure-volume ratio, or d(P/V)/dt<sub>max</sub> was determined. End-diastole was defined at the point at which d(P/V)/dt exceeded a 15% threshold of the maximal value. Ped was the pressure at that point.

**VED.** The maximum volume averaged over a 25 msec period, determined after flow (dV/dt) ceased.

**Time at end-systole (tes).** Time when the instantaneous pressure-volume ratio for each beat achieved a maximal value.

**Pes.** Pressure at time tes.

**End-systolic volume (Ves).** Minimum volume after tes, determined in the first 25 msec period after cessation of flow. This volume (as well as VED) was thus determined experimentally in a manner similar to that generally done clinically, i.e., minimum and maximum volumes measured during the isovolumetric period of the pressure-volume loop. For the theoretical analysis, Ves was presumed to be at the time of tes. These variables were used to calculate the following indexes.

**Ejection phase indexes**

**Ejection fraction.** Stroke volume/VED.

**Stroke work.** Integrated area within the pressure-volume loop.

**Stroke work/VED.** Stroke work divided by VED for each respective cycle.

**Mean systolic ejection rate (MSEr).** Stroke volume divided by systolic ejection period (SEP). SEP was measured from the onset to the cessation of ejection, with the use of dV/dt to determine ejection timing.

**Maximum velocity of circumferential shortening (Vcfm<sub>max</sub>).** Maximal value of the ratio: (−dV/dt)/V. Since V = (4/3)nrr<sup>3</sup> = (2πr)<sup>3</sup>/(16πr) = C<sup>3</sup>/6π<sup>2</sup>, where C = circumference. Thus (dV/dt)/V = [3C<sup>2</sup>−dC/dt]/C<sup>3</sup> = 3(dC/dt)/C.

**Isovolumetric phase indexes**

**(dP/dt)<sub>max</sub>.** Maximum value of the rate of change in pressure. Pressure was digitized at 200 Hz.

**(dP/dt)<sub>max</sub>/Ved.** dP/dt<sub>max</sub> divided by the VED for each respective cycle.

**(dP/dt)<sub>max</sub>/IP.** dP/dt<sub>max</sub> divided by the instantaneous developed isovolumetric pressure, or the pressure difference between Ped and the pressure at the time of dP/dt<sub>max</sub>.

**Pressure-volume relationship**

**ESPVR.** The point of maximal pressure-volume was first determined for each cardiac cycle. A least squares linear regression was applied generating slope (Ees) and intercept (Vo) estimates. With this Vo estimate, the points of maximal (P/V−Vo) for each cycle were obtained, and a second regression was used to determine new estimates for Ees and Vo. This process was continued until there was no further change in either parameter estimate with subsequent iterations.

**Statistical analysis.** Statistical analysis of load dependence was performed by one-way analysis of variance with repeated measures. The p values represent the general dependence (F-test) calculated with all of the data from each loading condition, and not simply paired comparisons of the highest and lowest loads. Alterations in contractility with inotropic stimulation were examined with paired t tests. Data are reported as the mean ± SEM.

**Results**

A total of 23 hearts were studied. Not all loading conditions or inotropic changes were tested in each heart. Data were selected for each set of loading conditions if they fulfilled the stability criteria for the preparation over the time period required to obtain the data (see Methods). Under control conditions with hearts ejecting against normal vascular impedance with an average heart rate of 117.6 ± 3.7 beats/min, the ESPVR had a mean slope of 4.87 ± 0.53 mm Hg/ml, a Vo of 5.1 ± 2.15 ml, and a correlation coefficient of 0.998 ± 0.005. The mean Ped was 16.1 ± 2.9 mm Hg, the mean ejection fraction 31.5 ± 3.9%, the mean peak left ventricular pressure was 115.4 ± 9.2 mm Hg, and the mean dP/dt<sub>max</sub> was 1473 ± 194 mm Hg/sec. Heart rate was kept relatively constant by atrial pacing throughout the study. These values, while somewhat low compared with those in ventricles in situ, are consistent with the denervated, isolated ventricular preparation.
Influence of preload change. Data for the indexes as well as hemodynamic variables at each of the four different preloads are provided in Table 1. Load 1 indicates low preload with a mean $V_{ed}$ of $24.3 \pm 2.9$ ml, while load 4 (high preload) was $41.0 \pm 1.1$ ml. An example of pressure-volume loops obtained under this load protocol is shown in figure 1, A. Figure 2 displays the data for ejection fraction, stroke work, MSER, and $V_{cf_{max}}$ while figure 3 shows the data for the isovolumetric indexes.

Ejection fraction displayed only a slight increase with an increase in $V_{ed}$ from $25.3 \pm 3.9\%$ at the low preload to $30.1 \pm 4.7\%$ at the high preload ($p = .094$) (figure 2, A). In contrast, stroke work displayed a much larger change, increasing nearly threefold from $664 \pm 206$ to $2102 \pm 475\$\text{mm Hg}\cdot\text{ml}$ ($p < .005$) over the same preload range (figure 2, B). When stroke work was divided by $V_{ed}$ this preload influence was reduced (table 1), but remained significant ($25.8 \pm 6.2$ to $30.1 \pm 11$, $p < .025$). MSER (figure 2, C) displayed a marked rise with increasing $V_{ed}$, whereas $V_{cf_{max}}$ showed a small but consistent decrease with rising preload (figure 2, D). Thus, among the ejection phase indexes, ejection fraction, stroke work/$V_{ed}$, and $V_{cf_{max}}$ were influenced relatively little by changes in preload volume, while stroke work and MSER were very sensitive to volume loading.

Figure 3, A, illustrates the influence of preload on the three isovolumetric indexes. Data were obtained from the same ejecting beats shown in figure 2. To enable display on a single graph, data are presented as percent change from the value at lowest load. With increasing preload, $dP/dt_{max}$ rose proportionately. When $dP/dt_{max}$ was divided by $V_{ed}$, this preload dependence was essentially eliminated. Division by the instantaneous developed pressure ($[dP/dt_{max}]/IP$) also led to a marked reduction in the load influence, but a small increase (18% from load 1 to load 4) persisted.

Figure 3, B, displays the same three indexes determined at four similar preload volumes, but in isovolumetrically contracting rather than ejecting hearts. The pattern of load dependence for each index was essentially identical to that observed in the ejecting hearts, confirming that these indexes were indeed measured in the isovolumetric phase of ejection, even over a wide preload range.

Influence of resistance change. Figure 1, B, illustrates an example of the pressure-volume loops generated by varying the resistance from 1.0 to 8.0 mm Hg·sec/ml while maintaining $V_{ed}$ constant. Table 2 lists the mean values of the contractile indexes for this load sequence. The mean values for the Ees and Vo of the ESPVR were $7.7 \pm 1.7\text{ mm Hg/ml}$ and 12.6 ml, respectively. While preload alteration over a physiologic range had little influence on ejection fraction (figure 2, A), the change in afterload resistance had a substantial effect, with a marked reduction in ejection fraction from $45.3 \pm 3.8\%$ at the lowest resistance, to $17.8 \pm 3.5\%$ at the highest resistance (figure 2, E). Stroke work (figure 2, F) displayed a curvilinear relationship that was rela-
FIGURE 2. Influence of preload alteration (A to D) and afterload resistance alteration (E to H) on four ejection phase indexes of contractile state. The four indexes shown are: ejection fraction (%), stroke work (SW, mm Hg·ml), MSER (ml/sec), and VCF<sub>max</sub> (sec<sup>-1</sup>). Data are mean ± SEM.

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tively insensitive to changes in resistance, but did suggest a reduction in stroke work at both extremes of low and high R. Stroke work divided by Ved was unchanged from this pattern since Ved was a constant in this protocol. Both MSER and VCF<sub>max</sub> were significantly reduced (by nearly 50%) with increasing resistance (figure 2, G and H).

The results for the isovolumetric indexes are shown.
A

FIGURE 3. Influence of preload (A) and afterload resistance (C) alteration on three isovolumetric phase indexes of contractile state. Changes with preload are shown for ejecting beats (A), and isovolumetric beats (B). Data are displayed as percent change, normalized to the index value at the lowest preload or afterload loading condition. The indexes shown are: dP/dt max (▲), dP/dt max/Ved (□), dP/dt max/IP (○).

in figure 3, C. Both dP/dt max and (dP/dt max)/Ved showed a similar curvilinear relationship with increasing resistance, with relatively less change when R was 4 mm Hg·sec/ml or more than when it was 4 or less. Thus, the influence of afterload resistance was not removed by normalization to Ved, whereas preload dependence was. However, division by instantaneous developed pressure reduced the influence of varying resistance, with nearly constant dP/dt max/IP for normal or high resistances (R = 4 or 8), and a gradual increase at lower resistances.

Influence of inotropic stimulation. The responses of the contractility indexes to increases in inotropic state pro-
duced by intracoronary infusion of calcium chloride or dobutamine are listed in table 3. Seven hearts were injected with each agent, and in several instances, both agents were administered to the same heart after reestabishment of a new baseline. All of the indexes demonstrated a significant increase with positive inotropic stimulation. The largest changes were found in dP/dt max and (dP/dt max)/Ved, stroke work, and stroke work/Ved, which increased by nearly 50% with calcium, and nearly 100% with dobutamine. In contrast, ejection fraction and MSER rose only 23% and 43% with the two agents, respectively. The ESPVR also shifted upward, but the extent of changes was relatively small compared with changes in several of the other indexes. Ees increased from 4.05 ± 0.34 to 4.82 ± 0.39 with calcium infusion (+19%) and from 3.93 ± 0.31 to 5.12 ± 0.51 with dobutamine (+30%). The tes decreased significantly (by about 10%) with both agents.

Theoretical analysis of contractility indexes. To further clarify the load and contractility dependence of the various indexes we undertook a theoretical analysis in which each index was expressed by variables common to pressure-volume relationships. The following principal expressions were used:

\[ \text{Pes} = \text{Ees} \cdot (\text{Ves} - \text{Vo}) = \text{Ees} \cdot (\text{Ved} - \text{SV} - \text{Vo}) \quad (1) \]
\[ \text{Pes} = \text{Ea} \cdot \text{SV} \quad (2) \]

where \( \text{Ea} \) = effective arterial elastance; \( \text{SV} \) = stroke volume. Equation 1 is the definition of the Ees in terms of the Pes and Ves, and the volume intercept Vo. This relationship can also be expressed as a function of Ved and stroke volume. Equation 2 expresses Ea, as defined by Sunagawa et al.,\(^{18}\) which has been experimentally shown to be approximately equal to the total vascular resistance \( R \) divided by the cycle length (T).\(^{18, 19}\) This measure provides an index of afterload resistance, and can be used along with the ESPVR and Ved to predict stroke volume. Pes in equation 2 represents arterial Pes, which is assumed to be approximately the same as ventricular Pes in equation 1. These two expressions contain variables of preload volume (Ved), afterload resistance (Ea), and contractility (Ees), and thus can be used to examine the relationships of other indexes to these variables. The following analysis assumes that Ees is relatively insensitive to both preload and afterload change. This has been shown to be a good approximation over a wide range of values in the isolated canine ventricle.

Ejection fraction. Combining equations 1 and 2 and rearranging (see Appendix 1) we get:
Ejection fraction = Ees \([1 - (V_o/V_e)] / (E_a + Ees)\) (3)

Figure 4 illustrates the dependence of ejection fraction on Ved, Ea, and Ees, respectively, in each case holding the other two variables (and V_o) constant. Values used for each variable are indicated in the figure. The analysis demonstrated that ejection fraction was relatively insensitive to changes in preload over a wide range, and that only at very low values of Ved (< 15 ml) did the hyperbolic relationship rapidly decline to zero. This pattern is very similar to what we observed (figure 2, A) experimentally; ejection fraction changed little over a physiologic preload range.

In contrast, changes in Ea produced a different hyperbolic relationship, with ejection fraction displaying a marked load dependence over a physiologic range of resistance values. Figure 4, B, shows this relationship at three different contractility levels (values of Ees). Ejection fraction was most sensitive to afterload with low contractility (Ees = 1), whereas at high contractility (Ees = 10), ejection fraction declined less and more gradually with increasing Ea.

The relationship between Ees and ejection fraction was also curvilinear, with small changes in ejection fraction when Ees fell to subnormal values. This is easily displayed by the first derivative curve of the relationship between ejection fraction and Ees (figure 4, C).

*Stroke work.* Stroke work is defined as the integrated area within the pressure-volume loop. Assuming a flat diastolic pressure-volume relationship and a relatively square shape for the pressure-volume loop, stroke work can be approximated by:

\[ SW \approx E_a \cdot V_o \cdot V_e^2 \] (by equation 2)

From equations 1 and 2, we find (Appendix 1) that:

\[ SW = E_a \cdot V_e \cdot (Ees/(Ea + Ees))^2 \cdot (V_e - V_o)^2 \] (5)

This expression demonstrates that stroke work will increase with the square of preload volume (Ved) (figure 5, A), and is thus very sensitive to filling volume. The curvilinearity is most prominent at low values of Ved. In a physiologic range (Pes \(\geq 60\) mm Hg, stroke volume \(\geq 10\) ml), which is shown as the space above the dashed line in figure 5, A, the stroke work vs Ved relationship becomes approximately linear. This linearity was apparent in the experimental data (figure 2, B), and has also been reported in a study of closed-chest dogs.\(^{20}\)

The dependence on Ea is displayed in figure 5, B. Assuming Ees, Ved, and V_o are constants, then for both very low and very high Ea, stroke work will fall, while within a broad operating range (3 \(\leq E_a \leq 8\)) the stroke work–Ea relationship is relatively flat (compare experimental data in figure 2, F). The maximal stroke work will occur when Ea = Ees (Appendix 1).

<table>
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<tr>
<th>Index</th>
<th>Load 1</th>
<th>Load 2</th>
<th>Load 3</th>
<th>Load 4</th>
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<td>2.0</td>
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<td>Ved</td>
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<td>36.8 ± 1.6</td>
<td>36.8 ± 1.5</td>
<td>36.4 ± 1.6</td>
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<td>SV</td>
<td>16.7 ± 1.6</td>
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<td>9.5 ± 1.4</td>
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<td>12.1 ± 4.5</td>
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<td>89.0 ± 6.5</td>
<td>114 ± 11.7</td>
<td>128 ± 15.5</td>
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<td>118 ± 7.4</td>
<td>118 ± 7.1</td>
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<td>ttes</td>
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<td>220 ± 24</td>
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<td>SEP</td>
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<td>Vcf(_{max})</td>
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<td>1072 ± 203</td>
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<td>(r^2)</td>
<td>.984 ± .005</td>
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Abbreviations are as in table 1.
Influence of inotropic stimulation on indexes of contractility

<table>
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<th>Control</th>
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<td>D</td>
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<td>33.8 ± 1.6</td>
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<td>C</td>
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<tr>
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<td>C</td>
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<td>11.3 ± 0.9</td>
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<td>Ped</td>
<td>D</td>
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<td>7.8 ± 2.1</td>
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<td></td>
<td>C</td>
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<td>C</td>
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<tr>
<td>EF</td>
<td>D</td>
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<td></td>
<td>C</td>
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<td>D</td>
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<td></td>
<td>C</td>
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<td>1960 ± 250</td>
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<td>SEP</td>
<td>D</td>
<td>164 ± 4.5</td>
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<td></td>
<td>C</td>
<td>162 ± 4.5</td>
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<td>C</td>
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<td></td>
<td>C</td>
<td>184.3 ± 3.6</td>
<td>171.8 ± 3.7</td>
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D = dobutamine HCl infusion; C = calcium chloride infusion; other abbreviations are as in table 1.
*p < .05.

Note: SW/Ved response similar to SW, since Ved was kept constant.

To assess the relationship between contractile state (Ees) and stroke work, equation 5 can be rearranged as:

\[ SW = \lambda [1/(1 + Ea/Ees)]^2 \]  \hspace{1cm} (6)

where \( \lambda \) equals \( Ea \cdot (Ved-Vo)^2 \). This relationship is displayed in figure 5, C. Also shown is the rate of change in stroke work as a function of Ees (Appendix 1), which demonstrates that stroke work increases most rapidly when Ees is low, while less change is predicted at high contractility states.

**MSER.** We define MSER = SV/t_s, where t_s is the systolic ejection period. Then by equation 5A (Appendix 1):

\[ MSER = [Ees/(Ees + Ea) \cdot (Ved - Vo)]/t_s \]  \hspace{1cm} (7)

While this simple analysis does not reveal a theoretical dependence of \( t_s \) on either Ved or Ea, we can use the results from the experimental data. From table 1, \( t_s \) increased from 158 to 185 msec when Ved rose from 24 to 40 ml. With the use of a linear model, we find that:

\[ t_s = 0.00169 \cdot Ved + 0.1175 \]  \hspace{1cm} (8)

In the physiologic range for Ved, this dependence on Ved is small, thus

\[ MSER \approx [Ees/(Ees + Ea) \cdot (Ved - Vo)]/0.1175 \]  \hspace{1cm} (9)

and MSER can be seen to be directly proportional to Ved, as was demonstrated experimentally and is illustrated, in figure 2, C.

For afterload dependence we refer to table 2 and find that \( t_s \) decreases with increasing Ea. Again applying a linear model we find:

\[ t_s = -0.0094R + 0.239 \]  \hspace{1cm} (10)

Thus:

\[ MSER \approx [Ees/(Ees + Ea) \cdot (Ved - Vo)]/0.239 \]  \hspace{1cm} (11)

and MSER is seen to be inversely proportional to Ea.

**Isovolumetric indexes.** The isovolumetric indexes can be assessed by differentiating the time varying elastance expression:

\[ P(t) = E(t) \cdot (V(t) - Vo) \]  \hspace{1cm} (12)

with a normalized expression for time varying elastance (Appendix 2). This yields:

\[ dP/dt_{max} = b \cdot (Ees/tes) \cdot (Ved - Vo) \]  \hspace{1cm} (13)

where \( b \) is a constant. We have found experimentally that tes changes only slightly with changes in preload (table 1). Thus, \( dP/dt_{max} \) was seen to vary linearly with Ved (figure 6, A). Normalizing \( dP/dt_{max} \) by Ved reduced this preload dependence, particularly when \( Vo << Ved \) (figure 6, B). However, in settings in which \( Vo \) is large relative to Ved, such as in dilated ventricles, then simple normalization by Ved will not be adequate. However, the slope of the \( dP/dt_{max} \)-Ved relationship would still be useful.21

If \( dP/dt_{max} \) is normalized by the instantaneous developed pressure (Appendix 3), we find:

\[ (dP/dt_{max})/IP = \Lambda/\alpha Ees \cdot [1/Ees'(t')] - \kappa Ved^\alpha/ (Ees (Ved - Vo)) \]  \hspace{1cm} (14)

where \( \Lambda, \kappa, \alpha \), and \( \alpha \) are constants. This theoretical depen-
reduces this sensitivity and makes the relationship more linear. By equation 14, $dP/dt_{\text{max}}/IP$ will increase if $tes$ and $'t$ decrease; however, the relative sensitivity to inotropic stimulation will be substantially blunted (figure 6, D).

The theoretical afterload dependence of $dP/dt_{\text{max}}$ can be evaluated if we model the normalized time varying elastance with a simple $\sin^2$ function (Appendix 3). We assume a square shape to the pressure-volume loop, and approximate the pressure at the onset of ejection with $P_{es}$. The time to reach a given $P_{es}$ can be solved in terms of the ventricular $E_{es}$ and $E_a$:

$$t = \left( \frac{1}{\theta} \right) \arcsin \left( \frac{E_a}{(E_a + E_{es})} \right)^{1/2}$$

We further assume that if $dP/dt_{\text{max}}$ occurs after this time, some ejection will have occurred, and make the amount of ejection a linear function of time, i.e.,

$$\text{ejected volume} = k \cdot t.$$ 

Solving for $dP/dt_{\text{max}}$, we find:

$$dP/dt_{\text{max}} = E_{es} \cdot \theta \cdot \sin \left( 20t \right) \cdot \left( V_{ed} + k \cdot (tes/2) - t \right) - V_o - \kappa \cdot \sin^2 \left( \theta t \right) \cdot E_{es}$$

where $\theta = \pi/(2 \cdot tes)$. Combining equations 15 and 16 we can examine the predicted changes in $dP/dt_{\text{max}}$ as a function of $E_a$. For $E_a \geq E_{es}$, $t$ will be $\geq tes/2$, and $dP/dt_{\text{max}}$ will occur before the onset of ejection. Thus, $\kappa$ is set to zero, and equation 16 simplifies to equation 13. If $E_a$ is $\leq E_{es}$ then some ejection will occur, and $dP/dt_{\text{max}}$ will no longer occur during the isovolumetric period. This result would hold for $dP/dt_{\text{max}}/Ved$ (figure 6, C) as well, since $Ved$ is constant. Normalizing $dP/dt_{\text{max}}$ by the instantaneous developed pressure (equation 22A, Appendix 2) yields a theoretical estimate of $dP/dt_{\text{max}}/IP$, and these results are also displayed in figure 6, C. Both of the model predictions are remarkably similar to the experimental data (compare with figure 3, C), displaying a 50% increase in $dP/dt_{\text{max}}/Ved$ from low to high $E_a$, and a smaller $\approx 25\%$ decrease in $dP/dt_{\text{max}}/IP$ over a similar load range.

**Discussion**

Numerous indexes have been proposed to assess left ventricular contractile strength; however, studies in animals and man have shown that no one index can be relied on under all operating conditions because of load dependencies. The present study directly compared multiple indexes in the controlled isolated ejecting canine ventricle, and examined the influence of preload volume, afterload resistance, and change in contractility. In agreement with previous studies, we found each index displayed certain strengths and weaknesses

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**FIGURE 4.** Theoretical dependence of ejection fraction on preload (A), afterload (B), and contractile state (C). Other variables assumed constant for each panel are: A. $E_{es}$ (5 mm Hg/ml), $E_a$ (4 mm Hg/ml), $V_o$ (2 ml); B. $V_o$ (2 ml), $V_{ed}$ (30 ml), $E_{es}$ (2 $\bullet$), 5 $\cdot$ , or 10 $\cdot$ [+] mm Hg/ml; C. $E_a$ (4 mm Hg/ml), $V_{ed}$ (30 ml), $V_o$ (2 ml). In C, both the dependence on $E_{es}$ (solid line) and the instantaneous slope of this relationship (dotted line) are displayed. See text for details.
range. Experimental and theoretical results were generally in close agreement.

The "relativeness" of load dependence. Some influence of altered loading on each index was demonstrated, but the extent and range of prominence of load dependence varied widely. The experimental data, and particularly the theoretical analysis, suggested that the nature of load dependence was often complex and nonlinear. This resulted in several indexes having significant dependence on preload or afterload, yet being relatively independent of load over a specified range.

Ejection fraction serves as a good example. The dependence on preload was small in the experimental data. The theoretical relationship between ejection fraction and Ved was markedly curvilinear at very low preload volumes, but within a physiologic operating range, the ejection fraction vs Ved curve was flat, displaying little load dependence. Thus, ejection fraction could be said to be relatively preload independent as long as filling volume is operating in the normal and supranormal range. The influence of afterload resistance, on the other hand, is more curvilinear within the normal physiologic range, and thus presents a greater limitation to the use of ejection fraction as a measure of ventricular contractile function. Even this limitation, however, is "relative," since the higher contractility, the less sensitive ejection fraction becomes to changes in afterload (figure 4, B), while greater sensitivity is predicted at low contractile states.

A similar analysis could be applied to stroke work. While the theoretical dependence of stroke work on Ved, Ea, and Ees were all curvilinear, the data within a physiologic operating range showed a fairly linear dependence on preload, a small variation with afterload resistance, and a fairly linear correlation to contractility (as indexed by Ees). These patterns were similar to what was found in the experimental data.

dP/dt max normalized either to Ved or instantaneous developed pressure (IP) was only minimally influenced by alterations in Ved over a wide range. However, afterload dependence was present at low values of Ea. Many investigators have found that in the physiologic range, the ventricle remains isovolumetric at least up to the time of maximum rate of pressure development, and thus this afterload dependence remains minimal. Therefore, both indexes would appear to be "relatively load independent" as long as the ventricle under study did not undergo any large reduction in afterload resistance.

Comparison of load dependence. Load dependence for all of the indexes could be contrasted by normalizing the percent change in each index from the lowest to the
highest load level (for preload and afterload respectively) by the percent change of the index with the greatest load sensitivity. This relative percent load dependence would therefore be 100% for the index with the greatest load influence, and 0% for an index with no load dependence. Figure 7 illustrates this relative load dependence for preload and afterload. In general, the indexes that show the least dependence on preload volume are influenced the most by changes in afterload, and vice versa.

The load dependence of the ESPVR was not examined in this study. We have previously reported, in the same preparation, data that demonstrate that the ESPVR is effectively load insensitive over load ranges similar to those used in the current study. There was a difference between the mean Ees for the data on changes in preload and those on afterload change (at constant preload). The greater slope observed in the latter is in part due to differences in the animals used, but is also consistent with a maximal amplification of previously reported small changes in the ESPVR with alterations in vascular impedance.

The ESPVR in situ may be more curvilinear than that observed in the isolated canine ventricle, and there is some evidence that afterload dependence may be greater.23 These differences would tend to further "linearize" relationships such as stroke work vs Ved,20 and would not influence dp/dtmax vs Ved relationships as markedly.21

"Relativeness" of inotropic sensitivity. The underlying strength of an inotropic index that serves to counter any load dependence is its sensitivity to altered contractility. An ideal index would display little significant load dependence in the physiologic range, but would also show a sensitive response to inotropic stimulation. Ultimately it is the balance of these two factors that determines the utility of any of the indexes. Figure 8 displays the relative sensitivity of each of the indexes to the infusion of dobutamine, normalized in a manner similar to that in figure 7. Perhaps the most striking result was that Ees demonstrated the smallest increase with inotropic stimulation. Stroke work, dp/dtmax, and dp/dtmax/Ved all displayed a relatively large increase, nearly three times that observed in Ees.

Figure 6. Theoretical dependence of isovolumetric phase indexes on preload (A and B), afterload (C), and contractile state (D). The indexes are individually labeled on each panel.
dobutamine and calcium), this slope would increase more than Ees alone. A similar result was noted in a recent study by Lee et al., \(^{17}\) in which it was concluded that dP/dt\(_{\text{max}}\) was as effective for defining increases in contractility as the ESPVR, but was also more sensitive to small inotropic changes.

The advantage of Ees is not in the absolute magnitude of its sensitivity to inotropic change, but in its minimal load dependence in the presence of both types of load alteration, combined with its adequate reflection of inotropic state. Modification of dP/dt\(_{\text{max}}\) by normalization to Ved substantially improved its preload dependence, without substantially altering its sensitivity to inotropic change. However, dP/dt\(_{\text{max}}\)/IP demonstrated a much smaller change than dP/dt\(_{\text{max}}\)/Ved, as predicted in figure 6, C. This is an example of a modification of an index (dP/dt\(_{\text{max}}\)) in which preload and afterload dependence is markedly reduced, but so is the sensitivity to changes in contractility.

Figure 9 displays the ratio of relative inotropic sensitivity to relative load dependence, a measure of the "predictive value" for each index. A high ratio indicates that a change in a given index likely reflects inotropic change rather than load change. Presented in this manner, Vcf\(_{\text{max}}\) is in one sense the best choice if there is no alteration in afterload, while stroke work and stroke work/Ved are superior if afterload is changing. Unfortunately, this graph presents idealized load alterations, and in vivo, changes in preload and afterload
are generally coupled. This ultimately limits the usefulness of $Vc_{\text{max}}$ and ejection fraction, for example, while indexes such as $dP/dt_{\text{max}}/V_{\text{ed}}$, which display little preload dependence, little afterload dependence in the physiologic range, and marked sensitivity to inotropic change, appear an excellent choice.

In conclusion, we examined multiple indexes of contractility to assess both experimentally and theoretically the precise nature of load dependence and comparative inotropic sensitivity. Nearly every index used to describe the inotropic state of the ventricle has an operative range of loading in which the sensitivity to load is minimal, and the index accurately portrays the contractile state. However, nearly all of the indexes display load sensitivity in one form or another, and in vivo, where afterload and preload changes are frequently coupled, this limits their utility. It should be noted, however, that these experimental results were generated in excised, denervated, isolated hearts, which generally have a lower contractile state than ventricles in vivo. As was shown for ejection fraction (figure 4, B), load dependency itself can be modified by the resting contractile state, and with greater $Ees$, dependence on load could well be less than we observed. Finally, the reputed “sensitivity” of the ESPVR lies largely in its minimal load dependence rather than the absolute magnitude of response to inotropic alteration.

References

13. Suga H, Sagawa K, Shoukas AA: Load independence of the instantaneous pressure-volume ratio of the canine left ventricle and effects

Appendix 1

Ejection fraction can be easily related to Ees, Ea, and Ved by use of equations 1A and 2A for the Ees and Ea:

\[ \text{Pes} = \text{Ees} \cdot (\text{Ved} - \text{SV} - \text{Vo}) \]  
(1A)

\[ \text{Pes} = \text{Ea} \cdot \text{SV} \]  
(2A)

Therefore:

\[ \text{Ea} \cdot \text{SV} = \text{Ees} \cdot (\text{Ved} - \text{SV} - \text{Vo}) \]  
(3A)

\[ (\text{Ea} + \text{Ees}) \cdot \text{SV} = \text{Ees} \cdot (\text{Ved} - \text{Vo}) \]  
(4A)

or:

\[ \text{SV} = \frac{\text{Ees} \cdot (\text{Ved} - \text{Vo})}{(\text{Ea} + \text{Ees})} \]  
(5A)

Since:

\[ \text{EF} = \frac{\text{SV}}{\text{Ved}} \]  
(6A)

then:

\[ \text{EF} = \text{Ees} \cdot [1 - (\text{Vo}/\text{Ved})]/(\text{Ea} + \text{Ees}) \]  
(7A)

Stroke work can be approximated by:

\[ \text{SW} \approx \text{Pes} \cdot \text{SV} = \text{Ea} \cdot \text{SV}^2 \]  
(8A)

By equation 5A,

\[ \text{SW} = \text{Ea} \cdot (\text{Ees}/(\text{Ea} + \text{Ees}))^2 \cdot (\text{Ved} + \text{Vo}) \]  
(9A)

The dependence of stroke work on the arterial elastance Ea can be better appreciated by rearranging 9A as:

\[ \text{SW} = \frac{\text{Ees}^2 \cdot (\text{Ea} + 2 \text{Ees} + \text{Ees}^2)}{\text{Ea}} \cdot (\text{Ved} - \text{Vo})^2 \]  
(10A)

Differentiating equation 9A with respect to Ea, and solving for d(Sw)/dEa = 0, we find that maximum stroke work occurs when:

\[ \text{Ees}^2 \cdot (\text{Ved} - \text{Vo})^2 \cdot (1 - 2\text{Ea} \cdot (\text{Ees} + \text{Ea})) = 0 \]  
(11A)

Appendix 2

We define a normalized time varying elastance E(t) as:

\[ \text{E}(t) = \frac{\text{Ees} \cdot \text{En}(t/\text{tes})}{\text{tes}} \]  
(15A)

where En is the normalized E(t) scaled between 0 and 1, and t/tes is the normalized time coordinate, also scaled between 0 and 1. Left ventricular pressure can be related to E(t) during the isovolumic phase (V(t) = Ved) by:

\[ \text{P}(t) = \text{Ees} \cdot \text{En}(t/\text{tes}) \cdot (\text{Ved} - \text{Vo}) \]  
(16A)

since the V = Ved during this period. Differentiation with respect to time yields:

\[ \frac{d\text{P}}{dt} = \text{Ees} \cdot (\text{Ved} - \text{Vo}) \cdot \frac{d\text{En}}{dt \times \text{tes}} \]  
(17A)

and

\[ \frac{d\text{P}}{dt_{\text{max}}} = \text{Ees} \cdot (\text{Ved} - \text{Vo}) \cdot \frac{d\text{En}}{dt_{\text{max}}} \]  
(18A)

where t* = t/tes. Since En(t*) is insensitive to load and contractile state by definition, dEn/dt*max is a constant (\Lambda). Therefore:

\[ \frac{d\text{P}}{dt_{\text{max}}} = \frac{\text{Ees} \cdot (\text{Ved} - \text{Vo}) \cdot \frac{d\text{En}}{dt \times \text{tes}}}{\text{tes}} \]  
(19A)

Rearrangement of equation 19A yields equation 13 in the text. The instantaneous developed pressure at the time of dP/dtmax can be modeled by a second elastance expression. If P' is the pressure at the time (t') of dP/dt_{max}, then:

\[ P' = \text{Ees} \cdot \text{En}(t') \cdot (\text{Ved} - \text{Vo}) \]  
(20A)

\[ \text{IP} = P' - \text{Ped} \]  
(21A)

Let Ped be described by a simple power function relationship

\[ \text{Ped} = \kappa \cdot \text{Ved}^\alpha \]  

Then:

\[ \text{IP} = \text{Ees} \cdot \text{En}(t') \cdot (\text{Ved} - \text{Vo}) - \kappa \cdot \text{Ved}^\alpha \]  
(22A)

Dividing equation 19A by equation 22A we get:

\[ \frac{d\text{P}}{dt_{\text{max}}} / \text{IP} = \frac{\Lambda \cdot (\text{Ees} \cdot \text{tes}) \cdot (\text{Ved} - \text{Vo})}{[\text{Ees} \cdot \text{En}(t') \cdot (\text{Ved} - \text{Vo}) - \kappa \cdot \text{Ved}^\alpha]} \]  
(22A)

Dividing by (Ved - Vo)-Ees we get:

\[ \frac{d\text{P}}{dt_{\text{max}}} / \text{IP} = \frac{\Lambda \cdot \text{tes} \cdot 1/[\text{En}(t') - \kappa \text{Ved}^\alpha]/(\text{Ees} \cdot \text{Ved} - \text{Vo})]} \]  
(24A)

This is equation 14 in the text.

Appendix 3

To evaluate the effect of afterload alteration on the isovolumic phase indexes let

\[ (\text{En}(t) = \sin^2 (t\theta) \]  
(25A)
where $\theta = \pi/(2 \cdot \text{tes})$ and cardiac cycle extends from $t = 0$ to $t = \text{tes}$. Substituting this into equation 15A (Appendix 2), we obtain:

$$E(t) = \text{Ees} \cdot \sin^2(\theta t) \quad (26A)$$

$$\frac{dE}{dt} = \text{Ees} \cdot 2 \theta \sin(\theta t) \cos(\theta t) = \text{Ees} \cdot \theta \cdot \sin(\theta t) \quad (27A)$$

$$\frac{dE^2}{dt^2} = 2 \theta^2 \text{Ees} \cdot \cos(2\theta t) \quad (28A)$$

Thus during isovolumetric contraction:

$$\frac{dP}{dt} = \text{Ees} \cdot (\text{Ved} - \text{Vo}) \cdot \theta \sin(2\theta t) \quad (29A)$$

The time of maximal $\frac{dP}{dt}$ will be when $\frac{dP^2}{dt^2} = 0$, or:

$$\text{Ees} \cdot (\text{Ved} - \text{Vo}) \cdot 2 \theta \cos(2\theta t) = 0 \quad (30A)$$

$$\cos(2\theta t) = 0 \quad (31A)$$

or

$$2\theta t = \pi/2 \quad (32A)$$

Since

$$\theta = \pi/(2 \cdot \text{tes}) \quad (33A)$$

then

$$t = \text{tes}/2. \quad (34A)$$

Assuming the pressure-volume loop is fairly rectangular, then Pes approximates the pressure at the onset of ejection. The time to reach a given ejection pressure ($\approx$ Pes) can be solved as a function of both Ees and Ea.

From equation 5A (Appendix 1)

$$\text{Pes} = (\text{Ea} \cdot \text{Ees}) \cdot (\text{Ved} - \text{Vo})/(\text{Ees} + \text{Ea}) \quad (35A)$$

However, from equations 15A (appendix 3) and 26A above,

$$\text{Pes} = \text{Ees} \cdot (\text{Ved} - \text{Vo}) \cdot \sin^2(\theta t) \quad (36A)$$

therefore

$$\sin^2(\theta t) = \text{Ea}/(\text{Ea} + \text{Ees}) \quad (37A)$$

and

$$t = (1/\theta) \arcsin(\text{Ea}/(\text{Ea} + \text{Ees}))^{1/2} \quad (38A)$$

If the time to reach Pes exceeds the time to reach $\frac{dP}{dt}_{\text{max}}$, then there will be little afterload dependence. If, on the other hand, $t < \text{tes}/2$, then some ejection will have occurred before $\frac{dP}{dt}_{\text{max}}$. Let the amount of volume ejected be a linear function of time. Then:

$$P(t) = E(t) \cdot (\text{Ved} - kt - \text{Vo}) \quad (39A)$$

Differentiating equation 39A and substituting equations 27A and 28A, we obtain:

$$\frac{dP}{dt}_{\text{max}} = \text{Ees} \cdot \theta \cdot \sin(2\theta t) \cdot (\text{Ved} - \kappa \cdot (\text{tes}/2 - t) - \text{Vo}) \quad (40A)$$

$$- \kappa \cdot \sin^2(\theta t) \cdot \text{Ees}$$
Comparative influence of load versus inotropic states on indexes of ventricular contractility: experimental and theoretical analysis based on pressure-volume relationships.


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