The relationship of various measures of end-systole to left ventricular maximum time-varying elastance in man

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ABSTRACT This investigation was designed to calculate left ventricular maximum time-varying elastance (E_max), to define the relationship between E_max and pressure-volume (P-V) relations at other, more easily defined measured of end-systole, and to determine whether these measures of left ventricular contractile function can be normalized in man. Accordingly, we studied 10 subjects with simultaneous high-fidelity micromanometer left ventricular and ascending aortic pressure recordings and biplane contrast cineangiograms at control conditions and during infusion of methoxamine and nitroprusside. E_max was defined as the maximum slope of the linear relation of isochronal, instantaneous P-V data points obtained from each of the three loading conditions. Left ventricular end-systole was also defined for each loading condition as: the time of the maximum P-V ratio (maxPV), minimum ventricular volume (minPV), (−)dP/dt_{min} [(−)dP/dt_{PV}], and zero systolic flow approximated by the central aortic dicrotic notch (AodiPV). The mean heart rates and LV (+)dP/dt_{max} were insignificantly altered during the three loading conditions. Isochronal E_{max} ranged from 3.38 to 6.73 mm Hg/ml (mean 5.48 ± 1.23 [SD] mm Hg/ml) and the volume-axis intercepts at zero pressure ranged from −2 to 51 ml (mean 18 ± 16 ml). The isochronal slope calculations were reproducible (r = .97 to .99). The end-systolic P-V slope values for the maxPV, minPV, (−)dP/dt_{PV}, and AodiPV relations correlated with isochronal E_{max} (r = .90, .88, .69, and .74, respectively). The average slope values for these end-systolic P-V relations, however, underestimated the mean E_{max} (p < .01 to p < .001). The mean extrapolated volume-axis intercepts for these end-systolic P-V relations also underestimated that for E_{max}. Finally, the isochronal E_{max} and other end-systolic P-V relation slope values demonstrated inverse linear relationships with left ventricular mass (r = −.68 to −.91, p < .05 to p < .001). Only the E_{max} volume-axis intercepts showed a linear relationship with left ventricular end-diastolic volume (r = .75). Thus we conclude that the time-varying elastic properties of the left ventricle can be calculated in man, that commonly used end-systolic P-V relations significantly underestimate isochronal E_{max}, and that normalization of isochronal E_{max} and other end-systolic P-V relation slope values might be performed in man with left ventricular mass; no obvious relationship between volume-axis intercepts and measures of left ventricular or body size was apparent.


THE EVALUATION of left ventricular contractile function by isovolumic or ejection phase indexes, which are variably affected by chamber loading conditions, is problematic.1,2 The linear relation between end-systolic pressure (stress) and volume (dimension) has been proposed as a load-independent measure of left ventricular contractile function.1–3 The linear relations of the time-varying relationship, E(t), of isochronal, instantaneous pressure [P(t)] vs volume [V(t)] data points is maximal near end-ejection. At a constant heart rate and with a stable contractile state, alterations in left ventricular preload, afterload, or both do not affect E_{max}.6

Since E_{max} represents a measure of left ventricular contractile function, several invasive and noninvasive studies in man have evaluated end-systolic P-V or pressure-dimension (P-D) relations.24–35 Although these initial human studies indicated that end-systolic
P-V or P-D relations might be useful for assessing left ventricular contractile function, important limitations of these investigations have been raised. The end-systolic P-V relations used in these studies were defined differently than isochronal E\textsubscript{max}. Important-ly, an attempt to calculate E\textsubscript{max}, defined as the maximum slope of the time-varying relationship of isochronal, instantaneous P-V data points, has been performed in only one study in man by means of radionuclide angiography. In contrast, no data exist regarding the calculation of isochronal E\textsubscript{max} with use of the superior spatial and temporal resolution of biplane contrast cineangiography. Whether a systemic relationship exists between P-V relations at various, more easily defined measures of end-systole and isochronal E\textsubscript{max} has not been completely defined in man. In some of these initial human studies, the end-systolic P-V relationship was generated from a single data point assuming a zero volume-axis intercept. This approach is not consistent with the physiologic concept, since end-systolic P-V relations are defined by both a slope and V\textsubscript{0} value generated from the linear regression of several data points. Finally, the potential independent influence of left ventricular and body size on time-varying elastance has been emphasized and demonstrated in animals. Although methods for normalizing E\textsubscript{max} and V\textsubscript{0} have been suggested, no data regarding this important issue are available in man. Accordingly, we have calculated the left ventricular maximum time-varying elastance using three biplane contrast cineangiograms during altered loading conditions; we have determined where relationships exist between isochronal E\textsubscript{max} and P-V relations obtained from more easily defined and frequently used measures of end-systole; and we have evaluated methods for the normalization of E\textsubscript{max} and other end-systolic P-V relation slope and V\textsubscript{0} values in man.

Methods

Patients. The study population consisted of 10 subjects with atypical chest pain, who were referred for diagnostic cardiac catheterization. Each subject gave written informed consent for this investigation on forms approved by the Institutional Review Board at the University of Michigan or University of Texas Health Science Center and/or Human Studies Committee at the VA Medical Center, Ann Arbor. There were five women and five men whose ages ranged from 36 to 60 years (mean 48 ± 8 [SD]). No subject had experienced a prior myocardial infarction. All 10 subjects had a normal electrocardiogram, physical examination, chest x-ray and M mode echocardiographic study. Before the cardiac catheterization, two subjects were taking no medications, whereas eight subjects were taking one or more of the following medications: diuretics (five subjects), nitrates (one subject), β-adrenergic blocking drugs (three subjects), calcium-entry blocking drugs (three subjects), and vasodilators (one subject). All diuretics, β-adrenergic blocking drugs, and vasoactive drugs were stopped 48 hr before the cardiac catheterization, and nitrates were stopped 12 hr before catheterization.

Protocol. After a diagnostic right and left heart catheterization had documented resting pressures, cardiac output, normal coronary anatomy, and negative ergonovine stimulation test, each subject entered the protocol, which consisted of the simultaneous recording of high-fidelity micromanometer pressures and biplane contrast cineangiograms at control conditions and during infusion of methoxamine and nitroprusside. The average infusion rate of methoxamine was 664 ± 460 μg/min (range 200 to 1500) and that of nitroprusside was 48 ± 17 μg/min (range 30 to 70). These infusion rates were adjusted in each patient to increase by 50 mm Hg or to decrease by 30 mm Hg, respectively, left ventricular peak pressure. A 15 to 20 min equilibration period was allowed between each cineangiogram to dissipate the hemodynamic effects of the contrast agent.

Hemodynamics. A bipolar pacing catheter was placed in the right atrium through the right femoral vein. Pacing was used to maintain heart rate constant during the three loading conditions. A NAMIC catheter was already in place in the left brachial artery and connected to a Statham P23Db transducer leveled at the midaxillary line to measure peripheral systemic arterial pressure. Through the right femoral artery, a calibrated high-fidelity dual pressure sensor micromanometer catheter (VPC-780C or VPC-684D, Millar Instruments, Houston) was positioned with the distal pressure sensor in the left ventricular chamber and the proximal pressure sensor in the ascending aorta. Both pressure sensors demonstrated no thermal drift during the study, since zero reference measurements before and after each hemodynamic recording were unchanged.

During each phase of the protocol, hemodynamic recordings were made with an Electronics for Medicine VR-16 or VR-12 physiologic recorder at 100 mm/sec paper speed with cine frame markers. Representative analog oscillograph recordings at 25 mm/sec of two electrocardiographic leads, high-fidelity micromanometer left ventricular pressure (50 and 200 mm Hg scales) and ascending aortic pressure (200 mm Hg scale), the first derivative of left ventricular pressure (dP/dt) obtained by continuous electronic differentiation of the left ventricular pressure signal, and left brachial artery pressure (200 mm Hg scale) appear in figure 1. The left ventricular pressure signals recorded during the control conditions and infusion of methoxamine and nitroprusside simultaneously with the biplane contrast cineangiograms were digitized with a Calcomp 9100 inductance digitizing surface (resolution 0.02 mm) interfaced to an IBM-PC computer. A program developed in our laboratory for this system has a variable sampling frequency for instantaneous left ventricular pressure and dP/dt. We sampled these data at approximately 5 msec intervals throughout the RR interval.

Cineangiography. To perform biplane contrast cineangiography, a pigtail catheter was inserted through the left femoral artery. Left ventricular biplane contrast cineangiograms were obtained in the 30 degree right anterior oblique and 60 degree left anterior oblique/20 degree cranial angulations (CGR-Dou-ble Angiomax) or the 30 degree right anterior oblique/60 degree left anterior oblique angulations (Phillips-Optimus 4000) after the injection of 36 to 50 ml of meglumine diatrizoate (Renogra-fin-76) at 60 frames/sec (16.7 msec sampling frequency). One of the first 3 beats after contrast injection, which did not follow a ventricular ectopic beat, was used for analysis. The initial frame at the peak of the R wave was taken as end-diastole, and the left ventricular silhouettes in each angulation were digitized frame-by-frame with a sonic digitizer (Science Accessories) mounted on a Vanguard XR-35 cine projector and interfaced to an IBM-PC computer. The long axes were measured in both projections from the left ventricular apex to the junction of the aortic and mitral valve planes. Then a modified Simpson's rule...
algorithm was used to calculate left ventricular volumes. This volumetric technique has been validated in comparison to absolute left ventricular human heart cast volumes obtained by water displacement \((r = .99\) for both, SEE = 7 and 5 ml, respectively) for the biplane oblique cineangiographic technique\(^{29}\) and biplane cineangiographic technique \((y = 6 + 0.91 \times)\). The left ventricular wall thickness was calculated by the technique of Hugenholtz et al.\(^{40}\) and the left ventricular mass was subsequently calculated by the approach of Rackley et al.\(^{41}\)

**Calculation of E\(_{\text{max}}\) and end-systolic pressure-volume relations.** With the corresponding high-fidelity micromanometer left ventricular pressure measurements and biplane contrast cineangiographic left ventricular volumes, isochronal instantaneous P(t) vs V(t) data points from the three loading conditions were linearly regressed at 16.7 msec intervals beginning at the R wave and continuing throughout the cardiac cycle. The maximum slope value obtained by linear regression analysis of these three P-V data points was defined as isochronal E\(_{\text{max}}\).

In each subject, there was a progressive increase in the slope values of the left ventricular time-varying elastance until E\(_{\text{max}}\) was reached, followed by a progressive decline in slope values. Pressure-volume loops constructed for each loading condition in a representative subject are shown in figure 2. A. The time-varying elastance in this subject appears in figure 2, B. E\(_{\text{max}}\) occurred at 309 msec, and it was 3.38 mm Hg/ml with an extrapolated volume-axis intercept at zero pressure \((V_0)\) of 31 ml.

Several definitions of end-systole were used to calculate end-systolic P-V relations for comparison with isochronal E\(_{\text{max}}\). These included the time of the maximum P-V ratio (maxPV) which occurs at the left uppermost corner of the P-V loops\(^{4, 15, 21-23, 30}\); minimum ventricular volume (minPV)\(^{26}\); \((-dP/dt)_{\text{max}}\) \([((-dP/dtPV)]^{35, 42}\); and zero systolic flow approximated by the central aortic dicrotic notch (AodiPV)\(^{24, 43}\).

The time of left ventricular \((-dP/dt)_{\text{max}}\) was obtained from the digitized left ventricular pressure signal. Other P-V relations that have been used in prior human studies were also evaluated, including ascending aortic peak (Aop) and dicrotic notch (Aodi) pressure vs minimum left ventricular volume (Aop/minV and Aodi/minV)\(^{20, 25, 28, 29, 35}\).

**Statistical analysis.** The hemodynamic data were analyzed

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**FIGURE 1.** Hemodynamic recordings obtained at 25 mm/sec at control conditions and during infusion of methoxamine and nitroprusside in a representative subject.

**FIGURE 2.** A. Pressure-volume loops constructed from pressure-volume data points every 16.7 msec at control and during infusions of methoxamine and nitroprusside in a representative subject. B. Time-varying elastance. Every isochrone beginning at frame 10 after end-diastole (R wave peak) is shown. Note the progressive increase in slope values from frame 10 to frame 19 (solid lines) and the subsequent decrease in slope values after E\(_{\text{max}}\) (dashed lines).
by an analysis of variance. When a significant F statistic was obtained, t tests with a Bonferroni correction were used to identify where differences occurred.

The three isochronal and end-systolic P-V data points in each patient were analyzed by least-squares linear regression analysis to obtain individual slopes and extrapolated volume-axis intercepts at V₀. Then the isochronal E max and end-systolic P-V slope and V₀ values in the 10 subjects were compared by least-squares linear regression analysis to obtain correlation coefficients (r), regression equations, and standard errors of the estimate (SEE).

The E max and end-systolic P-V relation data are presented as the mean ± SD and were compared by an analysis of variance. When a significant F statistic was obtained, t tests with a Bonferroni correction were again used to define where differences occurred. A probability value of .05 or less was considered significant.

Results

Hemodynamics (tables 1 and 2). The control hemodynamic data for each patient are shown in table 1, and the mean hemodynamic data for all 10 patients during the three loading conditions appear in table 2. The control heart rate was 78 ± 10 (SD) beats/min and did not vary significantly during the infusions of methoxamine and nitroprusside. In contrast, the mean control ascending aortic peak and dicrotic notch pressures were 122 ± 23 and 101 ± 15 mm Hg, and they increased during the methoxamine infusion to 181 ± 31 and 146 ± 21 mm Hg (p < .001 for both); they decreased during the nitroprusside infusion to 87 ± 13 and 72 ± 13 mm Hg (p < .001 for both).

The mean control left ventricular peak and end-diastolic pressures were 122 ± 24 and 12 ± 5 mm Hg, increasing during the infusion of methoxamine to 180 ± 32 and 19 ± 10 mm Hg (p < .001 and p < .01, respectively). The left ventricular peak pressure decreased during the infusion of nitroprusside to 93 ± 11 mm Hg (p < .001), whereas the left ventricular end-diastolic pressure decreased to 8 ± 6 mm Hg (p < .05). In contrast, the control left ventricular (+)dP/dt max was 1145 ± 342 mm Hg/sec and did not change during the infusions of methoxamine and nitroprusside. Similarly, the average (+)dP/dt normalized to develop pressure 40 mm Hg (DP40) during the control condition was 982 ± 327 mm Hg/sec, and it did not differ significantly during the infusions of methoxamine and nitroprusside (939 ± 370 and 1041 ± 341 mm Hg/sec, respectively).

The mean control left ventricular end-diastolic volume was 119 ± 43 ml, and it did not change significantly during the infusions of methoxamine and nitroprusside. In contrast, the mean control left ventricular

TABLE 1

<table>
<thead>
<tr>
<th>Subject</th>
<th>HR (beats/min)</th>
<th>LVP (mm Hg)</th>
<th>LVEDP (mm Hg)</th>
<th>(+)dP/dt max (mm Hg/sec)</th>
<th>EDVI (ml/m²)</th>
<th>ESVI (ml/m²)</th>
<th>EF (%)</th>
<th>LV massI (g/m²)</th>
<th>LV PWth (cm)</th>
<th>E max (mm Hg/ml)</th>
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<td>44.4</td>
<td>0.7</td>
<td>6.39</td>
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<td>17</td>
<td>835</td>
<td>84</td>
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<td>68.9</td>
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<td>1.0</td>
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<td>69</td>
<td>145.3</td>
<td>1.1</td>
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<td>5</td>
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<td>55</td>
<td>18</td>
<td>67</td>
<td>42.2</td>
<td>0.6</td>
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<td>9</td>
<td>75</td>
<td>134</td>
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<td>68</td>
<td>10</td>
<td>85</td>
<td>94.7</td>
<td>1.0</td>
<td>4.20</td>
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<tr>
<td>10</td>
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<td>34</td>
<td>10</td>
<td>69</td>
<td>47.0</td>
<td>0.8</td>
<td>6.66</td>
</tr>
</tbody>
</table>

Mean ± SD 78 ± 10 122 ± 24 11 ± 5 1145 ± 342 58 ± 26 19 ± 9 70 ± 8 77.2 ± 34.8 0.9 ± 0.2 5.48 ± 1.23

HR = heart rate; LVP = left ventricular peak pressure; LVEDP = left ventricular end-diastolic pressure; (+)dP/dt max = peak positive first derivative of left ventricular pressure; EDVI = left ventricular end-diastolic volume index; ESVI = left ventricular end-systolic volume index; EF = ejection fraction; LV massI = left ventricular mass index; LV PWth = cineangiographic end-diastolic left ventricular posterior wall thickness.

TABLE 2

<table>
<thead>
<tr>
<th></th>
<th>Mean heart rates, arterial and left ventricular pressures, and volumes (n=10)</th>
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<tbody>
<tr>
<td></td>
<td>HR (beats/min)</td>
</tr>
<tr>
<td>-------</td>
<td>----------------</td>
</tr>
<tr>
<td>Control</td>
<td>78 ± 10 (SD)</td>
</tr>
<tr>
<td>Methoxamine</td>
<td>77 ± 11</td>
</tr>
<tr>
<td>Nitroprusside</td>
<td>80 ± 13</td>
</tr>
</tbody>
</table>

AoP = ascending aortic peak pressure; Aodi = ascending aortic dicrotic notch pressure; other abbreviations as in table 1.

²p < .001; ²p < .05 vs control.
end-systolic volume was 35 ± 18 ml, increasing during
the infusion of methoxamine to 48 ± 19 ml (p < .001); it decreased during the infusion of nitroprusside
to 26 ± 16 ml (p < .001). The left ventricular ejection
fraction during the control condition was 70 ± 8%; it
decreased during the infusion of methoxamine to 64 ± 8%
(p < .01) and increased during the infusion of
nitroprusside to 76 ± 10% (p < .05).

The maximum time-varying elastance (E_max). The range
of isochronal E_max values in all 10 subjects was 3.38 to
6.73 mm Hg/ml (mean 5.48 ± 1.23). The individual
correlation coefficients for E_max ranged from .96 to
1.00 for each subject. The extrapolated volume-axis
intercepts ranged from −2 to 51 ml (mean 18 ± 16).
The time of occurrence of E_max (T_max) ranged from 262
to 383 msec (mean 327 ± 39).

Reproducibility. To determine the reproducibility of the
left ventricular maximum time-varying elastance
calculation, two patients underwent a frame-by-frame
analysis of left ventricular pressure and volume on two
different occasions. The correlation between iso-
chronal, instantaneous P-V slope values was .97 and
.99.

Comparison of end-systolic P-V relations to E_max (tables 3
and 4). The end-systolic P-V relations demonstrated
linear correlation coefficients for the slopes of the lines
connecting the three end-systolic P-V data points of
.87 to 1.00. The end-systolic P-V slope values for
maxPV, minPV, (−)dP/dtPV, and AodiPV correlated
with the slope values for isochronal E_max, (r = .90, .88,
.69, and .74, respectively, p = .02 to p < .001)
(figure 3). The AoP and Aodi/minV slope values also
correlated with isochronal E_max (r = .88 and .83, p = .001
and p < .01, respectively) (figure 4).

The average maxPV (4.05 ± 1.15 mm Hg/ml),
minPV (4.07 ± 1.14 mm Hg/ml), (−)dP/dtPV (2.71
± 1.18 mm Hg/ml), and AodiPV (3.29 ± 1.14 mm
Hg/ml) relations were all less than the mean E_max slope
value (p < .001 for all, figure 5). Similarly, the mean
extrapolated volume-axis intercepts for all of these
diastolic-P-V relations underestimated that for E_max,
but they did not reach significance because of the wide
variations in these values (figure 6). Similarly, the average AoP and Aodi/minV relations underestimated the mean $E_{\text{max}}$ slope value ($4.50 \pm 1.85$ mm Hg/ml, $p = .01$ and $3.52 \pm 1.42$ mm Hg/ml, $p < .001$, respectively); their mean $V_0$ values underestimated that for $E_{\text{max}}$, but again they did not reach significance (figures 5 and 6).

Normalization (tables 5 and 6). Several possible methods for normalizing isochronal $E_{\text{max}}$ and the other end-systolic P-V relation slope and $V_0$ values have been suggested or demonstrated in dogs, including left ventricular end-diastolic volume, body weight, body surface area, and left ventricular mass. The $E_{\text{max}}$ slope values correlated with both left ventricular mass and end-diastolic volume ($r = -.91$ and -.74, respectively, $p < .001$ and $p = .02$) (figure 7). When the other P-V relations were compared with these potential normalizing measures, the maxPV, minPV, and AoP

\[ n = 10 \\
\] \[ r = 0.90 \\
\] \[ p < 0.001 \\
\] \[ y = 0.96 + 0.94x \\
\] \[ SEE = 0.57 \\
\]

\[ n = 10 \\
\] \[ r = 0.69 \\
\] \[ p = 0.02 \\
\] \[ y = 0.92 + 0.66x \\
\] \[ SEE = 0.94 \\
\]

\[ n = 10 \\
\] \[ r = 0.68 \\
\] \[ p < 0.001 \\
\] \[ y = -0.40 + 0.82x \\
\] \[ SEE = 0.62 \\
\]

\[ n = 9 \\
\] \[ r = 0.74 \\
\] \[ p = 0.02 \\
\] \[ y = -0.31 + 0.65x \\
\] \[ SEE = 0.93 \\
\]

**FIGURE 3.** A, Maximum end-systolic P-V (maxPV) relations for all 10 subjects, on the ordinate, are compared with the $E_{\text{max}}$ values, on the abscissa. Individual points, correlation coefficient, regression equation, and standard error of the estimate (SEE) are shown. B, Pressure-volume slope values at minimum left ventricular volume (minPV), on the ordinate, are compared with the $E_{\text{max}}$ values, on the abscissa. C, Pressure-volume slope values at $(-)dP/d\min [(\ldots)dP/dPV]$, on the ordinate, are compared with the $E_{\text{max}}$ values, on the abscissa. D Pressure-volume slope values at zero systolic flow approximated by the aortic dicrotic notch (AodiPV), on the ordinate, are compared with the $E_{\text{max}}$ values, on the abscissa.
and Aodi/minV relation slope values also demonstrated a correlation with left ventricular mass (r = −.68 to −.84). No other significant correlations were observed (table 5). When the Vo values were evaluated in a similar manner, only one correlation was observed, and that was between the Emax volume-axis intercept and left ventricular end-diastolic volume (r = .75, p = .01, figure 8). No other significant correlations were noted (table 6).

**Discussion**

In the present investigation, we calculated the left ventricular maximum time-varying elastance (Emax) in man by means of simultaneous high-fidelity micromanometer pressure measurements and biplane contrast cineangiograms during three different loading conditions and demonstrated the reproducibility of this calculation in two of our subjects. In addition, we also showed that the mean slope values for the various end-systolic P-V relations all significantly underestimated the average isochronal Emax; their average Vo values also underestimated that for Emax. This was confirmed for the AoP and Aodi pressure vs minimum left ventricular volume relations. Despite the underestimation of isochronal Emax and the corresponding unstressed volume (Vo) by more widely utilized measures of end-systole, these measures were linearly related to the maximum time-varying elastance over a wide range of values. Finally, we demonstrated an inverse linear relationship between isochronal Emax and other P-V relation slope values and left ventricular mass, whereas no obvious relationship was identified between measures of left ventricular or body size and the Vo values in our subjects.

Comparisons between various end-systolic P-V relations have been previously investigated in the excised, supported canine left ventricular preparation and in man. Kono et al. reported that the slopes of the left ventricular peak pressure vs end-ejection volume relations overestimated (p < .001) and the end-ejection P-V relations underestimated (p < .001) and the left ventricular maximum end-systolic P-V relations. Similarly, Nivatpumin et al. using high-fidelity left ventricular pressures and end-systolic volumes from single-plane cineangiograms in man, observed that the peak aortic pressure vs end-systolic volume relations averaged 10% greater than the maximum P-V relations, but both values correlated (r = .99). Recently, using radionuclide angiography, McKay et al. reported that the peak pressure vs minimum ventricular volume and end-systolic P-V relations, defined at peak (−)dP/dt, correlated with Emax obtained from the linear regression of isochronal, instantaneous P-V data points (r = .87 and .91, respectively), but the end-systolic P-V relations overestimated isochronal Emax.

In the present investigation, in contrast to the findings of McKay et al., all definitions of end-systole yielded P-V relations that underestimated isochronal Emax. The relationship in our subjects, however, between the
maximal end-systolic P-V relations and the peak aortic pressure vs minimum ventricular volume and the end-ejection P-V relations were comparable to the findings of Kono et al. and Nivatpumin et al. In a preliminary report from our laboratory, isochronal E\textsubscript{max} calculated by radionuclide angiography underestimated but correlated (r = .98) with E\textsubscript{max} values obtained with biplane contrast cineangiography. The difference between our observations and those of McKay et al. may be related to the relative temporal and spatial resolution of the techniques used. At the higher sampling frequency (16.7 msec) of the cineangiographic technique used in this study, more steep E\textsubscript{max} slope values may have been identified because the point of maximum time-varying elastance may have been more closely approximated than by the radionuclide techniques, one sampling at 30 msec and the other at 60 msec. Thus, in the excised, supported canine left ventricular preparation and in man, end-systolic P-V relations defined differently than isochronal E\textsubscript{max} do not have comparable slope values. Nevertheless, these alternative, more easily calculated P-V relations may be able to assess left ventricular contractile function.

Because of the time-consuming data processing required to obtain the end-systolic P-V relations from multiple loading conditions, several investigators have attempted to analyze a single cineangiogram to obtain these data. McKay et al., using radionuclide angiography, reported a correlation (r = .76) between the maximal P-V ratio and isochronal E\textsubscript{max}, and they suggested that a single-beat maximal P-V ratio might be a reasonable approximation of E\textsubscript{max}. In contrast, Kono et al. reported that in the excised, supported canine left ventricular preparation, the maximal P-V ratio underestimated the slope of the maximum P-V relations (p < .01) and was load dependent. Similarly, Wisenbaugh et al., in an intact canine preparation, have demonstrated the load dependence of the single-beat maximal pressure (stress)-volume ratio, a finding we have also demonstrated in man. Since the maximal P-V ratio from a single beat demonstrates load dependence, three or more P-V data points should

![FIGURE 5](image-url) Mean slope values for E\textsubscript{max} and the maxPV, minPV, (-)dP/dtPV, AodiPV, AoP/minV, and Aodi/minV relations are shown as the mean ± SD. Significant differences for these P-V relations from E\textsubscript{max} are noted.

![FIGURE 6](image-url) Mean extrapolated volume-axis intercepts at zero pressure, V\textsubscript{0}, for each of these end-systolic P-V relations are compared with that for E\textsubscript{max}. Format as in figure 5.
TABLE 5
Normalization of slope values for $E_{\text{max}}$ and various pressure-volume relations (n = 10)

<table>
<thead>
<tr>
<th>Body weight (kg)</th>
<th>BSA (m²)</th>
<th>LV mass (g)</th>
<th>LVEDV (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$E_{\text{max}}$</td>
<td>-0.42</td>
<td>-0.60</td>
<td>-0.91 (p&lt;.001)</td>
</tr>
<tr>
<td>maxPV</td>
<td>-0.33</td>
<td>-0.47</td>
<td>-0.84 (p&lt;.01)</td>
</tr>
<tr>
<td>minPV</td>
<td>-0.36</td>
<td>-0.37</td>
<td>-0.37 (p&lt;.01)</td>
</tr>
<tr>
<td>(-)dp/dtPV</td>
<td>0.15</td>
<td>-0.10</td>
<td>-0.54</td>
</tr>
<tr>
<td>AoP/minV</td>
<td>-0.11</td>
<td>-0.25</td>
<td>-0.64</td>
</tr>
<tr>
<td>AoP/minV</td>
<td>-0.12</td>
<td>-0.07</td>
<td>-0.75 (p = .02)</td>
</tr>
<tr>
<td>AoP/minV</td>
<td>-0.09</td>
<td>-0.17</td>
<td>-0.68 (p&lt;.05)</td>
</tr>
</tbody>
</table>

Correlation coefficients are shown with values noted in parentheses.
BSA = body surface area; LVEDV = left ventricular end-diastolic volume; other abbreviations as in preceding tables and text.

$n = 9$.

probably be obtained in any one patient to characterize end-systolic P-V relations by a slope and V₀ value, regardless of the definition of end-systole.²⁻⁶

It has been emphasized that the slope and V₀ values in man should be normalized to enable comparisons of left ventricular contractile function to be made between patient groups, since left ventricular size may have an independent influence on these values.¹⁷ Belcher et al.¹⁷ have examined this issue in an intact canine preparation and reported that the maximum end-systolic P-V relation slope and V₀ values correlated linearly with both body and left ventricular weight. The data in our subjects suggests that isochronal $E_{\text{max}}$ and other end-systolic P-V relation slope values might be normalized by left ventricular mass. However, the appropriate method for normalizing V₀ remains unclear.

Although our data indicate that $E_{\text{max}}$ can be calculated in man, certain potential limitations to this approach must be considered. First, our patients were studied with autonomic reflexes intact. Mehmel et al.²⁹ used propranolol and atropine to autonomic block adrenergic and muscarinic receptors in patients before calculating end-systolic P-V relations during cineangiography. Recently, Kass et al.⁴⁷ in an intact canine left ventricular preparation, calculated the maximum end-systolic P-V relations during full autonomic blockade and without autonomic blockade and demonstrated lower slope values after autonomic blockade caused by a reduction in inotropic state. We observed

TABLE 6
Normalization of volume axis intercept values for $E_{\text{max}}$ and various pressure-volume relations (n = 10)

<table>
<thead>
<tr>
<th>Body weight (kg)</th>
<th>BSA (m²)</th>
<th>LV mass (g)</th>
<th>LVEDV (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$E_{\text{max}}$</td>
<td>0.50</td>
<td>0.62</td>
<td>0.48</td>
</tr>
<tr>
<td>maxPV</td>
<td>0.34</td>
<td>0.47</td>
<td>0.09</td>
</tr>
<tr>
<td>minPV</td>
<td>0.31</td>
<td>0.45</td>
<td>0.05</td>
</tr>
<tr>
<td>(-)dp/dtPV</td>
<td>0.59</td>
<td>0.53</td>
<td>0.15</td>
</tr>
<tr>
<td>AoP/minV</td>
<td>0.33</td>
<td>0.31</td>
<td>-0.07</td>
</tr>
<tr>
<td>AoP/minV</td>
<td>0.25</td>
<td>0.21</td>
<td>-0.18</td>
</tr>
<tr>
<td>AoP/minV</td>
<td>0.29</td>
<td>0.23</td>
<td>-0.17</td>
</tr>
</tbody>
</table>

Abbreviations as in table 5.

$n = 9$. 

FIGURE 7. A, $E_{\text{max}}$ slope values for all 10 subjects, on the ordinate, are compared with the corresponding left ventricular mass determinations, on the abscissa. The individual points, correlation coefficient, regression equation, and standard error of the estimate (SEE) are shown. B, $E_{\text{max}}$ slope values, on the ordinate, are compared with the corresponding left ventricular end-diastolic volumes (LVEDV), on the abscissa.
FIGURE 8. Relationship between the $E_{\text{max}}$ volume-axis intercepts, $V_0$, on the ordinate, and the corresponding left ventricular end-diastolic volume values (LVEDV), on the abscissa. The individual points, correlation coefficient, regression equation, and standard error of the estimate (SEE) are shown.

no significant change in the average heart rate, left ventricular (+)dP/dt$_{\text{max}}$, and left ventricular (+)dP/dt/DP40 during the three loading conditions, which might have affected the calculation of $E_{\text{max}}$ and the other end-systolic P-V relations.$^{48,49}$ Thus, although we cannot completely exclude reflex changes in autonomic tone during the prolonged infusion of the vasoactive agents in this invasive study, these data would suggest that a relatively stable contractile state was maintained over the range of loading conditions used in this investigation. Moreover, since our subjects were not autonomically blocked, the $E_{\text{max}}$ and other end-systolic P-V relation slope and $V_0$ values should reflect basal left ventricular contractile function.

We altered load by infusing an arteriolar vasoconstrictor, methoxamine, and an arteriolar and venous vasodilator, nitroprusside. Sodums et al.$^{21}$ reported that an arteriolar vasoconstrictor shifted the left ventricular end-systolic P-V relation from that observed during control conditions. Although the slope of these relations did not change, the extrapolated volume-axis intercept was significantly smaller. The reason for this shift has been explained by Maughan et al.$^{50}$ as a closer approximation of the isovolumic length-tension relationship as arterial load is increased and a falling off of the isovolumic length-tension relationship as vasodilation occurs. This probably relates, in some degree, to the extent of ejection and flow in the unloaded condition.$^{51,52}$ However, these changes are small ($\leq 3$ ml), and in man, minor shifts in the end-systolic P-V relations observed over the limited range of loading conditions in this investigation are probably undetectable. Furthermore, isochronal $E_{\text{max}}$ and the maximal end-systolic P-V relations in the excised, supported canine ejecting left ventricle were generated during alterations in resistive afterload and were shown to be comparable to the isovolumic length-tension relations during control and altered contractile states.$^{5}$ In this study, isochronal $E_{\text{max}}$ and the other end-systolic P-V relations were similarly generated in man.

Another important consideration is the methods we used to define end-systole. In practical terms, end-systole has long been defined as end-ejection, although end-ejection may not under all hemodynamic conditions coincide with the end of left ventricular contraction.$^{53,54}$ Since the timing of end-ejection can be variably affected by alterations in left ventricular loading conditions, we chose isochronal $E_{\text{max}}$ as our operational definition of end-systole.$^{6,9,12,17}$ Several measures of left ventricular end-ejection were then compared with $E_{\text{max}}$, including the time of the maximum relationship of pressure to volume,$^{4,15,21-23,30}$ minimum ventricular volume,$^{26}$ ($-)$dP/dt$_{\text{min}}$, and zero systolic flow approximated by the aortic dicrotic notch pressure.$^{24,43}$ It was observed that the mean slopes of these end-systolic P-V relations all differed from each other and significantly from isochronal $E_{\text{max}}$. Nevertheless, these end-systolic P-V relations were each linearly related to $E_{\text{max}}$ over a range of values.

Based on the observations in this investigation, two important questions arise: why do the slope values for the end-systolic P-V relations underestimate isochronal $E_{\text{max}}$, and why do negative $V_0$ values occur? Several factors may contribute to these observations. One factor may be how the slopes are calculated. Isochronal $E_{\text{max}}$ is a time-dependent function, since isochronal, instantaneous P-V data points are used to calculate slope values throughout the cardiac cycle irrespective of the loading conditions. In contrast, all of the other end-systolic P-V relations are relatively time independent. Consequently, the timing of these events varies depending on the loading condition. This means that end-ejection will, in general, occur earlier and further from end-systole after the initiation of left ventricular contraction in the unloaded (nitroprusside) compared with the control and loaded (methoxamine) conditions. Additionally, Suga et al.$^{55}$ have recently reported in the excised, supported puppy left ventricle that the isovolumic P-V relations are convex upwards, plateauing at higher left ventricular pressures. This, however, was not shown for the adult animal left ven-
tricular preparation; consequently, whether this saturation effect occurred in our subjects over the physiologic pressure range used is unclear. Finally, Freeman et al. have shown that maximal end-systolic P-V relations produced by inferior venocaval occlusion have a lower slope during an infusion of methoxamine compared with those during control or during infusion of nitroprusside. Thus all of these factors may contribute to the lower end-systolic P-V relation slope values compared with isochronal E\textsubscript{max}.

These factors may also explain, in part, the observation that many of the end-systolic P-V relations have negative values for the unstressed volume. In only one of our subjects with a small left ventricular volume was V\textsubscript{0} less than zero for isochronal E\textsubscript{max}; then, it was only — 2 ml, which is within the variability of the cineangiographic method of obtaining left ventricular volumes. In contrast, as many as one-third of all the other end-systolic P-V relations had negative V\textsubscript{0} values outside the error of the volumetric method. This may be related to the reduced slope values resulting from the pharmacologic intervention. Alternatively, investigators have suggested that P-V data points in the physiologic range are linear, while in the subphysiologic range a curvilinear relationship may exist. Thus the linear extrapolation of the isochronal E\textsubscript{max} and end-systolic P-V relation slope values to zero pressure with only three P-V data points may not provide physiologically meaningful data. This may also explain why we observed no relationship between the V\textsubscript{0} values and left ventricular and body weight in our subjects.

Finally, to use the regression equations generated in this investigation to “normalize” isochronal E\textsubscript{max} and the other end-systolic P-V slope values for intergroup comparisons, one must assume that our subjects represent a relatively “normal” population. Since our subjects were studied for atypical chest pain, we cannot totally exclude occult cardiomyopathy, hypertrophy, or small- vessel coronary artery disease. Our subjects, however, were similar to those considered “normal” in other cineangiographic studies by left ventricular volume indexes, ejection fraction, wall thickness, and mass criteria. Only subject 7 fell outside 2 SDs of the “normal” mean value for left ventricular mass, which by cineangiography has a standard error of the estimate of 23 g. Nevertheless, even with subject 7 excluded, isochronal E\textsubscript{max} continued to correlate with left ventricular mass (r = — .86, y = 7.57 — 0.014x) but not with body weight or left ventricular end-diastolic volume. Thus the range of normalizing values observed in our subjects probably represents that of relatively “normal” men and women undergoing cardiac catheterization.

We conclude from these data that isochronal E\textsubscript{max} can be calculated in man, that other end-systolic P-V relations significantly underestimate isochronal E\textsubscript{max} and the unstressed volume, and that the most appropriate normalization of isochronal E\textsubscript{max} and end-systolic P-V relation slope values may be left ventricular mass; however, the appropriate normalization of V\textsubscript{0} remains unclear. Nevertheless, the various end-systolic P-V relations and the relationship of ascending aortic and dicrotic notch pressure to minimum left ventricular volume may be useful approximations of isochronal E\textsubscript{max}, and they may further simplify the acquisition of a relative measure of left ventricular contractile function in man. Whether the responses of these measures to positive and negative inotropic interventions are similar to those of isochronal E\textsubscript{max} remains to be evaluated.

We appreciate the technical assistance of Ming-Li Lui, Betty Heyl, Heather Varnum, Sheila Squicciarini, and Dan Montgomery in the acquisition and processing of these data, and the secretarial assistance of Diane Bauer in the preparation of the manuscript.

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Circulation. 1987;76:32-43
doi: 10.1161/01.CIR.76.1.32

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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