Sensitivity of End-systolic Pressure-Dimension and Pressure-Volume Relations to the Inotropic State in Humans

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SUMMARY The value for the slope of the left ventricular (LV) end-systolic pressure-dimension and pressure-volume relations has been proposed as a quantitative measure of the LV inotropic state. This measure of LV inotropic state is attractive because it is independent of preload and incorporates afterload. To investigate the sensitivity of the slope of these relations to alterations in contractile state, 10 normal subjects were studied using M-mode echocardiographic, phonocardiographic and indirect carotid pulse recordings during infusion of methoxamine to alter end-systolic pressure and during infusion of dobutamine (5 μg/kg/min) to increase LV inotropic state. Heart rate was maintained within a narrow range for each subject. End-systolic volume was calculated from end-systolic echocardiographic dimension by standard methods. End-systolic pressure was estimated from the dicrotic notch pressure determined from a calibrated carotid pulse recording; peak systolic pressure was also measured. Regardless of the method of approximating end-systolic pressure, the positive inotropic intervention caused a leftward shift in the end-systolic pressure-dimension and pressure-volume lines. With the dobutamine infusion, the value for the slope of the end-systolic pressure-dimension relation increased by 25% (range 16–46%, p < 0.001), while the slope of the end-systolic pressure-volume relation increased by 55% (range 37–85%, p < 0.001). In all cases, the curves were linear and became steeper with the positive inotropic intervention. In contrast, the value of the slope of the peak systolic pressure–end-systolic dimension relation showed a variable response to the dobutamine infusion (mean change 13%, range −77% to 73%; NS). Although the position of the peak systolic pressure–end-systolic dimension curve is consistently shifted with an alteration in inotropic state, the values of the slope of these curves are not reliable indicators of change in LV contractility. The values for the slope of the line relating end-systolic pressure (estimated by dicrotic notch pressure) to end-systolic dimension or volume, however, are highly sensitive to a change in inotropic state in human subjects.

THE MOST COMMONLY used measurements of left ventricular (LV) systolic function are the angiographic or radionuclide ejection fraction (EF) and the echocardiographic percent fractional shortening. These ejection phase indexes, however, are affected by changes in preload and afterload as well as by alterations in left ventricular contractility.1,2 The LV end-systolic pressure (PES)–end-systolic volume (VES) relation has been proposed as a more reliable index of events occurring at the level of the LV muscle fiber. This relation has none of the limitations of the ejection phase indexes because it is independent of preload, incorporates afterload, and varies directly with alterations in myocardial contractile state.3,4 To make the PES–VES relation more clinically applicable, several investigators have substituted the ventricular end-systolic dimension (DSS) for volume6–7 and peak systolic pressure (PSP) for PES.8–10 The curves relating pressure to volume or dimension at end-systole are thought to be linear over the physiologic range. The value for the slope of these end-systolic relations has been suggested as a numerical expression of myocardial contractility.11,12 However, Mahler et al.,6 studying conscious dogs, found that a positive inotropic intervention produced a leftward but parallel shift of the PES–DSS line.6 Grossman and co-workers,12 studying LV function in humans undergoing cardiac catheterization, demonstrated that the slope of the PES–VES line was considerably steeper for the normal than for the poorly contracting left ventricle, and suggested that the value for the slope of the relation could be used to assess myocardial contractile performance. In a series of studies in conscious dogs, Sagawa et al.7 found that an increase in ventricular contractility produced a leftward displacement of the PES–VES line and a variable change in slope. Thus, whether the slope alone reflects changes in LV inotropic state is not known.

We recently reported a safe, easily performed, non-invasive method of assessing LV function at end-systole.13 In the current investigation, we used this method to investigate the reliability of the PES–VES, PES–DSS and PSP–DSS relations as indicators of LV contractile state in humans. This was accomplished by studying normal subjects during infusion of methoxamine, a pure α-adrenergic agonist with no direct cardiac effect,14,15 and during infusion of dobutamine, a positive inotropic agent.16,17

Methods

Our study population consisted of 10 normal subjects, ages 21–32 years. The subjects had no history of cardiovascular disease, normal physical examinations and normal intracardiac anatomy by M-mode echocardiography, and were taking no medications.
An Irex Continutrace model 101 recorder and ultrasound module with a 2.25-MHz transducer was used for the M-mode echocardiographic recordings. An external microphone was placed at the right upper sternal border for phonocardiographic recordings. P 

PSS 

and diastolic blood pressure were measured with the Dinamap 845 Vital Signs Monitor (Critikon Inc.). In a comparative study between indirect brachial artery pressure readings using this instrument and simultaneous central aortic pressure measurements in 30 patients undergoing cardiac catheterization, this device accurately estimated central aortic pressure over a wide range of systolic (98–177 mm Hg) and diastolic (41–97 mm Hg) pressures. The mean absolute pressure differences and percent errors (pressure difference divided by central aortic pressure) were 0.8 mm Hg and 1% for systolic and 1.7 mm Hg and 2% for diastolic pressures, respectively (fig. 1). Dinamap estimations of central aortic pressure were not significantly influenced by cardiac index, systemic vascular resistance, LVEF, heart rate, or body surface area. Thus, we could obtain accurate noninvasive estimations of central aortic pressure.

Subjects were premedicated with atropine, 0.01 mg/kg, to abolish reflex cardiac slowing. Each subject underwent simultaneous recordings of systolic and diastolic blood pressure, echocardiogram of the left ventricle, phonocardiogram (PCG), indirect carotid pulse tracing (CPT), and ECG under baseline conditions. Blood pressure was then elevated by i.v. infusion of methoxamine at 1 mg/min until PSS had increased at least 30 mm Hg above the resting value. The methoxamine was discontinued and when systolic blood pressure had decreased by 15–20 mm Hg below peak value, an i.v. infusion of dobutamine hydrochloride (Lilly Inc.), 5 μg/kg/min, was begun. As the pressor effect of methoxamine was decreased by metabolism of the drug, the LV response to the positive inotropic intervention was recorded over a range of afterload conditions. Although recordings were made while systemic blood pressure both increased and decreased, we previously demonstrated that PSEDVSED and PSEDVSED relations show no hysteresis effect in normal subjects. For a given inotropic state, a heart rate variation of 10 beats/min or more was grounds for exclusion of data.

The echocardiographic LV DED was measured at the onset of the Q wave of the ECG, while DES was measured at the time of the first high-frequency component of the second heart sound. The measurements for DES and DED were taken as the mean value for five cardiac cycles. LV fractional shortening (%ΔD) was calculated as

\[ \frac{\text{DED} - \text{DES}}{\text{DED}} \]

LV VES and VED were estimated from echocardiographic dimensions using the method of Teichholz et al., which assumes that the visualized portion of the LV is representative of global LV function, an assumption shown to be valid in normal subjects in the absence of LV asynergy. LVEF was calculated as

\[ \frac{\text{VED} - \text{VES}}{\text{VED}} \]

The CPTs were calibrated by the automated blood pressure monitor device using the method of Stefanoudos et al. Systolic pressure was assigned to the peak and diastolic pressure to the nadir of the CPT. PES was estimated by linear interpolation to the height of the dicrotic notch. This method has been validated in our laboratory for systolic, diastolic, and dicrotic notch arterial pressures against an intrarterial standard (r = 0.97). Simple linear regression (least-squares method) was used to fit each subject's data to a pressure-dimension (PES = mDES + b; PPS = mDPS + b) or pressure-volume (PES = mVES + b) equation, where m = slope and b = y-intercept. The x-intercept (i.e., x value when

![Figure 1](https://example.com/figure1.png)

**Figure 1.** The relationship between central aortic (PAO) and Dinamap (PDIN) measurements for (A) systolic and (B) diastolic pressures. The linear regression equation that best predicted central aortic pressure from Dinamap reading and its correlation coefficient are given. The solid line is the line of identity and the dashed line is the least-squares regression line.
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**TABLE 1. Individual Response to the Positive Inotropic Intervention**
The responses of the 10 normal subjects to the control and dobutamine infusions are shown in table 1. Heart rate during the control state was 88 ± 21 beats/min, compared with 97 ± 20 beats/min during dobutamine infusion (p < 0.05). The ranges for \( P_{ES} \) during control and dobutamine infusions were similar, as were the ranges of values for \( D_{ES} \), \( D_{ED} \), and \( V_{ES} \) increased linearly with \( P_{ES} \) and for each subject were uniformly smaller during dobutamine than during control conditions. \( D_{ED} \) was significantly smaller (3.25 cm vs 3.65 cm) for dobutamine than control conditions despite the same \( P_{ES} \) (fig. 2). For all subjects, \( D_{RD} \) and \( V_{RD} \) got larger as \( P_{ES} \) increased. The increase in \( V_{RD} \) was generally comparable to the increase in \( V_{ES} \), and each subject's LV stroke volume was relatively unchanged for a given contractile state. The LV stroke volume during dobutamine infusion (80 ± 12 ml) was 23% higher than that during control conditions (65 ± 11 ml, p < 0.01). There was an inverse correlation between percent fractional shortening (and EF) and \( P_{ES} \). For any \( P_{ES} \), the percent fractional shortening and EF were higher during the dobutamine infusion than during the control state.
End-systolic Pressure-Dimension Relation

The PES-DES relation was linear for each subject fitting the equation \( P_{ES} = mD_{ES} + b \) with linear regression coefficients ranging from 0.958–0.996 (average \( r = 0.977 \)) for the control conditions and from 0.911–0.996 (average \( r = 0.965 \)) during dobutamine infusion (table 2). Figure 3 shows \( P_{ES} \) plotted against \( D_{ES} \) for each subject’s control and increased LV contractile state. In every case, dobutamine caused a leftward shift of the \( P_{ES}-D_{ES} \) relation such that at any \( P_{ES}, D_{ES} \) was smaller. The value of the slope of this relation was 104 ± 13 mm Hg/cm for the control and 129 ± 15 mm Hg/cm for the dobutamine condition (\( p < 0.001 \)), resulting in a mean increase of 25% (range 16–46%). In all 10 subjects, the curves became steeper with the positive inotropic intervention. The extrapolated \( D_o \) (i.e., \( D_{ES} \) when \( P_{ES} = 0 \)) was consistently smaller for the dobutamine data than for the control data (2.3 ± 0.2 cm vs 2.0 ± 0.3 cm, \( p < 0.05 \)).

End-systolic Pressure-Volume Relation

The \( P_{ES}-V_{ES} \) relation was also linear for each subject and fitted the equation \( P_{ES} = mV_{ES} + b \), \((r = 0.966–0.993 \) for the control and \( r = 0.909–0.992 \) for the dobutamine data (table 2). Figure 4 shows each subject’s \( P_{ES} \) plotted against \( V_{ES} \) for the different LV contractile states. As with the \( P_{ES}-D_{ES} \) relation, the dobutamine caused a leftward shift of the \( P_{ES}-V_{ES} \) line, resulting in a smaller \( D_{ES} \) for any \( P_{ES} \). The value of the slope of the \( P_{ES}-V_{ES} \) relation was 3.1 ± 0.5 mm Hg/ml for the control and 4.8 ± 1.1 mm Hg/ml for the dobutamine states (\( p < 0.001 \)), resulting in a mean increase of 55% (range 37–85%). Once again, the curves uniformly became steeper with the positive inotropic intervention. The extrapolated \( V_o \) (i.e., \( V_{ES} \) when \( P_{ES} = 0 \)) did not change with the dobutamine infusion (10 ± 6 cm vs 9 ± 6 cm, NS).

Peak Systolic Pressure–End-systolic Dimension (Volume) Relations

The \( P_{PS}-D_{ES} \) relation was linear for each subject during control conditions (average \( r = 0.969 \), range 0.957–0.997) and fit the equation \( P_{PS} = mD_{ES} + b \). During the dobutamine infusion, however, the linear regression coefficients ranged from 0.291 (subject 5) to 0.991 (subject 10) (mean 0.866 ± 0.220) (table 2). In figure 5, \( P_{PS} \) is plotted against \( D_{ES} \) for each subject during control and dobutamine conditions. Although the curves were consistently displaced to the left, there was a variable response in the value for the slope of the curves, as demonstrated by an increase in six subjects, no change in two subjects and a decline in the other two subjects. The value of the slope of the \( P_{PS}-D_{ES} \) relation during control conditions was 108 ± 14 mm Hg/cm (range 84–131 mm Hg/cm). During dobutamine infusion, the mean value of the slope was 125 ± 62 (range 24–227; NS vs control). The average percent change in the slope value with the positive inotropic intervention was 13% (range -77% to 73%). Thus, the slope of the \( P_{PS}-D_{ES} \) relation was an unreliable indicator of change in LV inotropic state. The extrapolated \( D_o \) was generally shifted to the left with the dobutamine infusion. However, because of the negative dimension for \( D \) in patient 5, no meaningful
statistical analysis regarding the relative position of \( D_0 \) under control and dobutamine conditions was possible.

When \( V_{ES} \) was substituted for \( D_{ES} \), the value for the slope of the \( P_{P,s}-V_{ES} \) curve and the extrapolated \( V_0 \) remained insensitive to changes in inotropic state.

### Discussion

This study demonstrates that both the position and the slope of the line relating \( P_{ES} \) (estimated by the aor-
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The relationship between end-systolic pressure ($P_{es}$) and end-systolic dimension ($D_{es}$) for the 10 subjects. Individual data points are shown for control (C) and increased contractile states. In every case, dobutamine (D) caused a leftward shift in the $P_{es}$-$D_{es}$ relation while increasing the value of the slope of the curve.

FIGURE 3.

The relationship between end-systolic pressure ($P_{es}$) and end-systolic volume ($V_{es}$) for the 10 study subjects. Individual data points are shown for control (C) and increased contractile states. Dobutamine (D) uniformly caused a leftward shift in the $P_{es}$-$V_{es}$ relation while increasing the value of the slope of the curve.

FIGURE 4.

dropic notch pressure) to LV $D_{es}$ or $V_{es}$ are highly sensitive to a positive inotropic intervention in human subjects. Although the position of the $P_{ps}$-$D_{es}$ (or $V_{es}$) curve is shifted to the left with dobutamine, the values of the slopes of these curves did not reliably indicate change in LV contractility.

In isolated cardiac muscle, the force-length curve produced by isometric contractions from a constant initial fiber length is shifted to the left with a positive inotropic stimulus and to the right with a negative inotropic stimulus. A similar response was shown in studies using isolated canine hearts in which LV active force-length curves were produced by variably afterloaded isovolumic contractions. When these studies were extended to the ejecting heart, the isovolumic and isometric force-length (or pressure-volume) curves were virtually identical and thus either one could be used to assess ventricular contractility. This fundamental principle of cardiac muscle physiology is the basis for the use of the $P_{es}$-$V_{es}$ relation as a measure of LV inotropic state that is independent of preload and mode of contraction but incorporates afterload. Canine studies have shown that the $P_{es}$-$V_{es}$ relation is also sensitive to changes in contractile state because $V_{es}$ and $D_{es}$ are linearly related over the physiologic range in the symmetrically contracting heart.

When we used either volume or dimension in the construction of our subjects' active force-length curves, the $P_{es}$-$V_{es}$ and $P_{es}$-$D_{es}$ relations were equally sensitive to LV contractile state, provided dicrotic notch pressure rather than $P_{ps}$ was used as a noninvasive estimate of LV $P_{es}$. Under basal conditions, the $P_{ps}$-$D_{es}$ and $P_{ps}$-$V_{es}$ relations were linear ($r > 0.950$) and had comparable slopes ($104 \pm 13$ mm Hg/cm vs $108 \pm 14$ mm Hg/cm, NS). This reflects the relatively constant absolute difference between peak systolic and dicrotic notch pressures over a large range of afterload conditions when LV contractility is normal. When ventricular contractility was increased with dobutamine, the $P_{ps}$-$D_{es}$ relation remained linear in all cases ($r > 0.910$), but the $P_{ps}$-$V_{es}$ relation became nonlinear ($r = 0.29$, $r = 0.758$) for two of the 10 subjects. In addition, the slope of the $P_{es}$-$V_{es}$ line showed a variable response to dobutamine: the
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mained from a calibrated CPT appears, in such cases, to be a more reliable and reproducible estimate of actual P_{ES} than is P_{PS}. The shape of the CPT closely resembles the central aortic pulse contour and accurately reflects pressure changes in the proximal aorta.  

V_{o} and D_{o} have been considered as possible additional indexes of LV contractility because they might reflect the ventricle's maximal pumping capacity. Some studies in dogs and in humans showed that V_{o} and D_{o} decreased as contractile state was increased. However, Sagawa et al. found no change in V_{o} and D_{o} in dogs when LV contractile state was enhanced by intracoronary infusion of isoproterenol. Our findings of no significant change in V_{o} and only minimal absolute change in D_{o} (range 0.0–0.6 cm) with dobutamine are in agreement with these latter studies.

Methodologic Considerations

Our noninvasive technique of assessing LV contractility function appears to be safe and is easy to perform. Since there is no hysteresis effect to the P_{ES}-V_{ES} relation in normal human subjects over a wide range of P_{ES}, the studies can be performed while afterload is gradually increasing or decreasing. The close correlation between dimension and volume over the physiologic range in patients without regional asynergy makes accurate noninvasive estimation of LV volumes possible. The ability of an automated blood pressure device to accurately estimate central aortic pressures as frequently as every minute makes repetitive, accurate estimation of aortic dicrotic notch pressure feasible. It also allows careful monitoring of P_{PS} without an intraarterial catheter.

Although no direct hemodynamic correlations for the end-systolic force-length relations were obtained in our study, we compared our results with those obtained by Grossman and co-workers in our cardiac catheterization laboratory. The value for the slope of the P_{ES}-V_{ES} curve (normalized for body surface area) determined using our noninvasive technique was 5.3 ± 0.5 mm Hg/ml/m², compared with 4.9 ± 1.7 mm Hg/ml/m² (NS) using direct pressure measurements and angiographically determined LV volumes. The mean value for V_{o} was also similar for the two studies (17 ± 11 ml/m² vs 23 ± 18 ml/m² (NS). Thus, the results obtained noninvasively closely correlate with values obtained by catheterization.

Our noninvasive technique for determining P_{ES}-D_{ES} and P_{ES}-V_{ES} has potential limitations. First, we assumed that LV contractility remained uniform under the various loading conditions. Although methoxamine has no direct cardiac inotropic effect, we cannot exclude the possibility of centrally mediated reflex changes in LV contractility. However, this possibility appears unlikely because heart rate remained relatively constant as afterload was altered and centrally mediated reflexes make at most a small contribution to the resting inotropic state in normal human subjects. Second, we used the first high-frequency component of the aortic second heart sound as a uniform marker to identify the timing of minimal

Figure 5. The relationship between peak systolic pressure (P_{PS}) and end-systolic dimension (D_{ES}) for the 10 subjects. Individual data points are shown for the control (C) and increased contractile states. Although dobutamine (D) consistently caused the curves to be displaced to the left, there was a variable response in the value of the slope of the curve, which increased in subjects 1, 2, 6, 7, 8 and 9, did not change in 3 and 10, and decreased in 4 and 5.

steepness of the curve increased in six cases, did not change in two and declined in the others. The loss of linearity in subjects 4 and 5 and the insensitivity of the numerical value of the slope of the P_{PS}-D_{ES} relation in subjects 3, 4, 5 and 10 may reflect factors that specifically affect P_{PS}, including the rate of LV ejection, LV stroke volume, and systemic vascular resistance. Dobutamine increases LV ejection velocity and stroke volume while decreasing systemic vascular resistance. It is thus possible that LV pressure peaks early in systole and declines rapidly during middle to late systole, resulting in a large disparity between peak and actual end-systolic pressures. A similar phenomenon has been described when isoproterenol is infused in normal subjects. This may be explained by LV ejection dynamics in humans, which are primarily inertial and are governed by the laws of mass acceleration. The dicrotic notch pressure deter

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LV D\textsubscript{RS}. This seemed reasonable because in the absence of mitral regurgitation, LV ejection is complete by the onset of A\textsubscript{2}. Third, we assumed that the echocardiographic D\textsubscript{RS} used in this study was representative of actual end-systolic fiber length. All of our subjects had normal LV size and contractility and no LV dilatation or hypertrophy, so geometric factors should not significantly bias our results. Fourth, we used the LV pressure at end-ejection to approximate true P\textsubscript{RS}. Although the aortic dicrotic notch pressure may slightly underestimate the LV pressure when minimal ventricular dimension is initially attained, our study suggests that it reliably and reproducibly estimates P\textsubscript{RS}. Unlike P\textsubscript{RS}, the aortic dicrotic notch pressure does not appear to be significantly affected by factors such as LV peak ejection rate. Finally, aortic dicrotic notch pressure may not provide a valid estimate of LV P\textsubscript{RS} in certain disease states such as aortic stenosis (where LV pressure generally exceeds aortic pressure throughout systole), aortic regurgitation (where it may be difficult to identify a dicrotic notch in the carotid pulse tracing), and mitral regurgitation (where LV volume may continue to decrease even after aortic valve closure).

Clinical Implications
In our subjects, the elevation of afterload with methoxamine caused an increase in end-systolic fiber lengths and a decline in percent fractional shortening and EF in accordance with the inverse force-shortening principle. The increases in V\textsubscript{ES} were balanced by comparable elevations of V\textsubscript{ED}, which resulted in maintenance of a constant stroke volume. This is the expected response to an afterload challenge in patients with normal myocardial function in the euvolemic state.\textsuperscript{11, 12} Patients with relative hypovolemia, diminished preload reserve, or LV systolic dysfunction respond to a moderate pressor challenge with a decrease in stroke volume and an exaggerated decline in the extent of systolic fiber shortening (afterload mismatch).\textsuperscript{23} Similarly, EF or percent fractional shortening may remain normal despite significant LV systolic dysfunction in patients with aortic or mitral regurgitation who have markedly increased preload.\textsuperscript{24} The seeming independence of the P\textsubscript{RS}-V\textsubscript{ES} or P\textsubscript{RS}-D\textsubscript{RS} relations from abnormal loading conditions should make these noninvasively determined indexes of myocardial contractile function more clinically useful than the standard ejection phase indexes in patients with either afterload mismatch conditions or marked derangements of preload from LV volume overload. In addition, this noninvasive technique may be useful in assessing the effects of pharmacologic interventions on left ventricular contractile state, as well as detecting preclinical left ventricular dysfunction in patients at risk of developing congestive heart failure.\textsuperscript{25, 26}

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