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Application of End-Systolic Pressure-Volume and Pressure-Wall Thickness Relations in Conscious Dogs

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The usefulness of end-systolic measures of ventricular function was compared with that of standard contractility indexes in conscious dogs. End-systolic relations between left ventricular pressure and volume and between pressure and wall thickness were analyzed in dogs previously instrumented with ultrasonic crystals. Progressive angiotensin infusions were used to generate computer-averaged pressure-volume and pressure-wall thickness loops. Both relations were linear in every study and highly reproducible.

With low and high dose dobutamine, the end-systolic pressure-volume relations were significantly displaced, with increased slope and inconsistent changes in intercept. This relation was more useful than the ejection fraction for detecting contractility increases at different afterloads, but it showed no advantage over maximal left ventricular dP/dt at all ranges of preload and afterload. The end-systolic pressure-volume relations were insensitive for detecting mild decreases in inotropic state produced by propranolol, and maximal dP/dt was superior for detecting such mild acutely reduced contractility. The end-systolic pressure-wall thickness relations showed displacement with dobutamine, although slope and intercept changes were not significant; these relations did not detect mild decreases in contractility produced by propranolol.

It is concluded that the end-systolic pressure-volume relation and a simplified end-systolic measure using pressure and wall thickness provide sensitive, load-independent and reproducible approaches for defining acute increases in left ventricular contractility in conscious animals. Maximal dP/dt was equally effective for defining these increases in contractility and more sensitive for detecting slight acute decreases in contractility.

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The end-systolic pressure-volume relation as proposed by Suga and Sagawa (1) has been shown to be a reliable method for characterizing changes in myocardial contractility in isolated hearts under controlled conditions (1–3). Several studies have applied various end-systolic measures for the assessment of left ventricular contractile properties in the intact animal (4–6) and in human subjects (7–12). In addition, some investigators (13,14) have used pressure-wall thickness or pressure-segment length relations for assessing regional contractility changes.

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Previous studies have not assessed the reproducibility of these relations in the intact state, nor have they been compared with standard contractility indexes for detecting modest changes in inotropic state. Therefore, the goals of this study in conscious dogs were to: 1) examine the reproducibility of end-systolic pressure-volume relations on the same day; 2) compare end-systolic relations with other measures of cardiac function for detecting changes in myocardial contractility; and 3) determine whether a simplified end-systolic measure, the regional end-systolic pressure-wall thickness relation, can be applied for characterizing the global contractile state.

Methods

Surgical preparation. Eleven adult mongrel dogs weighing 21 to 43 kg (mean 28) were anesthetized with sodium pentobarbital. Respiration was maintained by a Harvard respirator delivering room air through an endotracheal tube. A left thoracotomy was performed in the fifth intercostal space, the pericardium was opened and a high fidelity

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micromanometer (Konigsberg P-7) was inserted through the apex of the left ventricle. A Tygon tube (1.27 mm inner diameter) was also positioned in the left ventricular chamber to obtain zero reference and to calibrate the micromanometer. A Statham P23Db transducer was used to measure left ventricular pressure from the fluid-filled catheter and was calibrated before each experiment against a water manometer, with zero reference taken at the estimated level of the right atrium.

For measurement of the external left ventricular short axis, a pair of crystals (8 mm in diameter) was sutured to the epicardium of the anterior and posterior walls. A second pair of crystals (8 mm in diameter) was sutured to the base and apex of the left ventricle to measure the external left ventricular long axis. The base crystals were placed in the groove between the left atrium and the aortic root, and the other crystal at the apical dimple (15). A third pair of crystals was implanted on opposing sites across the myocardium of the left ventricular free wall to measure the wall thickness. The endocardial crystal was inserted through a diagonal tract, and the epicardial crystal was sutured to the site at which the ultrasonic transit time was the shortest (5). The pericardium was left open. All wires and tubing were passed subcutaneously to the back and exteriorized.

Experimental protocol. After complete recovery from the operation (at least 7 days), all experiments were performed in the conscious state with the animal resting quietly on its right side on a table. Control recordings at rest were made for spontaneous sinus rhythm during a steady state. Then, various afterloading conditions were induced by a stepwise angiotensin infusion (angiotensin II) (16), starting with 0.1 to 0.3 μg/min. Each step lasted at least 2 minutes to obtain a steady state, and recordings were made before increasing to the next angiotensin infusion rate. The infusion of angiotensin was stopped when the dog became restless; the maximal rate of angiotensin infusion in individual experiments varied between 0.6 and 2.0 μg/min. The duration of angiotensin infusion averaged 11.8 minutes.

In seven dogs, angiotensin infusion was repeated 30 minutes to 2 hours later without any inotropic intervention to examine reproducibility on the same day. In seven dogs, enhanced inotropic state was produced by means of dobutamine infusion. The infusion rate of dobutamine was adjusted to obtain an increase of the maximal first derivative of left ventricular pressure (dP/dt) of less than 50% (range 14 to 47%, mean 29%; 0.9 to 4.3 μg/kg per min, low dose). At the end of the angiotensin infusion, the dobutamine infusion was also stopped. At least 30 minutes later when the animal had returned to a stable state, the dobutamine infusion was repeated at a higher rate (2.8 to 10.9 μg/kg per min, high dose) to obtain a further increase of maximal dP/dt, averaging 67% (range 56 to 99%), and an angiotensin infusion was again performed. In six dogs, another angiotensin infusion was performed as a control when stable conditions had resumed after dobutamine infusion was discontinued; in the seventh dog, the positive inotropic interventions were performed after a single control angiotensin infusion.

In five dogs, after a control angiotensin infusion, the infusion was repeated after the contractile state was mildly depressed by injection of propranolol (1 mg/kg); maximal dP/dt was decreased by 5 to 17% (mean 11%) from the control value.

Data analysis. All data were recorded during the experiment on an eight channel Brush chart recorder and stored on a Hewlett-Packard magnetic tape recorder (HP model 3955D). The taped data were played back and digitized every 5 ms on a computer-assisted system (DEC PDP 11/03) (13,17). Calibrations were performed for each channel separately by providing a low and high level signal as reference points to the computer. After the calibration procedure, the high gain of the high fidelity pressure was matched to the left ventricular high gain pressure from the fluid-filled catheter to correct for drift. This pressure match was repeated several times during each experiment. At least 10 consecutive beats were digitized at a sampling interval of 5 ms and averaged to compensate for beat to beat variations. All data of the averaged beats were stored on a floppy disk for further computation.

The measured wall thickness was used to obtain the internal long and short axes of the left ventricle by subtraction from external diameters (15): LAD = LAD ext − 1.1 × WTH and SAD = SAD ext − 2 × WTH, where LAD = left ventricular internal long axis (mm); LAD ext = left ventricular external long axis (mm); WTH = free wall thickness of the left ventricle (mm); SAD = left ventricular internal short axis (mm); and SAD ext = left ventricular external short axis (mm).

Left ventricular volume (V) and circumferential wall stress (WSt) were calculated assuming a prolate ellipsoid in each animal at 5 ms intervals using the following equations (15,17,18):

$$V = \frac{\pi}{6} \times (LAD) \times (SAD)^2,$$

$$WSt = \frac{P \times (SAD)}{2 \times WTH} \times 1 - \frac{(SAD)^2}{2 \times (LAD)^2}.$$

The variables analyzed were left ventricular pressure, left ventricular dP/dt, left ventricular volume and circumferential wall stress. The first derivative of the left ventricular pressure (dP/dt) was obtained by use of an active differentiating circuit and was calibrated against a triangular wave of known slope. For assessment of the three-dimensional geometry of the left ventricle, two reference points were used during all experiments. Point 1 = end-diastole, determined at the time the first derivative of the left ventricular pressure (dP/dt) started its rapid upstroke; and Point 2 = end-systole, corresponding to end-ejection, taken at

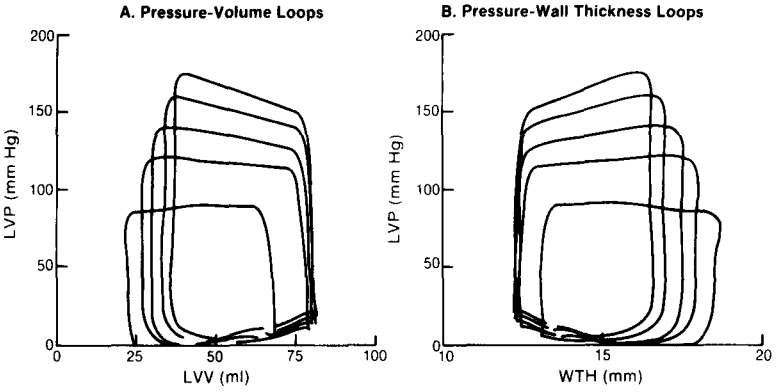


Figure 1. Representative example of left ventricular pressure (LVP)-volume (LVV) loops (**A**) and left ventricular pressure-wall thickness (WTH) loops (**B**) obtained by graded angiotensin II infusion from one experiment. Each loop is the computer-generated average of more than 10 cardiac cycles. Note the good linearity of the relation at end-ejection in both pressure-volume loops and pressure-wall thickness loops.

Table 1. Hemodynamic and Ventricular Volume Data Without Angiotensin Infusion

	Reproducibility (n = 7)		Propranolol (n = 5)		Dobutamine (n = 7)		
	Control 1	Control 2	Control	Propranolol	Control	Low Dose Dobutamine	High Dose Dobutamine
HR	101 ± 4	99 ± 10	90 ± 13	87 ± 10	99 ± 11	102 ± 12	111 ± 15
p		NS		NS		NS	NS
p′							NS
LVP ED	10.9 ± 2.3	11.4 ± 2.2	10.9 ± 3.4	13.2 ± 5.6	10.2 ± 2.8	12.5 ± 6.0	12.9 ± 4.1
p		NS		NS		NS	NS
p′							NS
Peak LVP	118 ± 20	119 ± 19	118 ± 10	119 ± 12	116 ± 21	129 ± 27	140 ± 29
p		NS		NS		<0.01	<0.01
p′							<0.05
dP/dt							
(+)	2,686 ± 412	2,565 ± 525	2,988 ± 545	2,653 ± 421	2,681 ± 554	3,366 ± 723	4,332 ± 970
p		NS		<0.05		<0.01	<0.01
p′							<0.01
(−)	−1,931 ± 476	−1,890 ± 426	−2,348 ± 259	−2,243 ± 264	−1,855 ± 465	−2,217 ± 672	−2,512 ± 626
p		NS		<0.05		<0.05	<0.01
p′							NS
LVV							
ED	76.5 ± 25.2	76.4 ± 29.3	66.2 ± 13.2	69.1 ± 11.0	70.9 ± 33.7	70.0 ± 35.0	70.6 ± 32.5
p		NS		NS		NS	NS
p′							NS
ES	40.1 ± 20.6	40.8 ± 21.4	34.4 ± 6.4	37.5 ± 6.2	37.6 ± 23.9	35.1 ± 22.6	32.1 ± 21.1
p		NS		<0.05		NS	<0.01
p′							<0.05
SV	36.1 ± 7.1	35.6 ± 8.6	31.8 ± 8.1	31.6 ± 7.1	33.3 ± 10.3	34.9 ± 13.2	38.6 ± 12.7
p		NS		NS		NS	<0.01
p′							NS
EF	49.4 ± 9.4	48.4 ± 7.1	47.9 ± 4.5	45.6 ± 5.2	49.9 ± 8.8	52.4 ± 7.8	57.4 ± 9.5
p		NS		NS		<0.05	<0.01
p′							NS
WST							
Peak	238 ± 96	240 ± 105	240 ± 50	251 ± 60	227 ± 115	253 ± 133	272 ± 135
p		NS		NS		<0.05	<0.01
p′							NS
Mean	186 ± 89	191 ± 94	188 ± 40	201 ± 46	182 ± 101	199 ± 114	206 ± 117
p		NS		NS		<0.05	<0.01
p′							NS

Control 1 = before the first angiotensin II infusion; Control 2 = before the second angiotensin II infusion on the same day; dP/dt = first derivative of left ventricular pressure; ED = end-diastolic; EF = ejection fraction (%); ES = end-systolic (= end-ejection); HR = heart rate (beats/min); LVP = left ventricular pressure (mm Hg); LVV = left ventricular volume (ml); Mean = mean ejection phase circumferential wall stress; p = probability versus control 1, or control; p′ = probability versus low dose dobutamine; peak = peak systolic; SV = stroke volume (ml); WSt = circumferential wall stress (g/cm^2); (+) = peak positive left ventricular dP/dt; (−) = peak negative dP/dt. Data presented as mean ± standard deviation.

the maximal excursion of the left ventricular volume curve within 20 ms before maximal negative dP/dt. Mean wall stress during ejection (mean WSt) was computed in each dog during the period from maximal positive dP/dt (max dP/dt) to the end of ejection.

Pressure-volume (Fig. 1A) and pressure-wall thickness loops (Fig. 1B) were generated by a computer-aided digital plotter from averaged beats. The relations between left ventricular pressure and volume, or pressure and wall thickness, at the end of ejection were plotted at several points during each progressive angiotensin infusion, and the linearity, slope and intercept were determined. To further compare the displacement of two individual relations, we computed the end-systolic volume or wall thickness at a constant left ventricular pressure (mean end-systolic left ventricular pressure of the control relation produced by angiotensin infusion). These mean (± standard deviation) end-systolic pressures were 86 ± 20, 91 ± 11 and 92 ± 23 mm Hg for angiotensin infusions during control, propranolol and dobutamine infusions, respectively.

Measurements of the ejection fraction before and after angiotensin infusion were compared at three stages in each group of experiments: before (Table 1) and at minimal and maximal doses of angiotensin infusion. For comparisons during control, low dose and high dose dobutamine and after propranolol, an analysis was also done over a range of mean wall stress values because dobutamine infusion resulted in a considerable change in left ventricular systolic pressure.

End-systolic wall stress values were also computed; although lower, the magnitude of their directional changes with drugs and angiotensin were similar and did not differ statistically from the mean wall stress values presented.

Statistical analysis. Overall statistical analysis of treatment effects was done using repeated measures analysis of variance (19). When significance was achieved, Tukey's

Table 2. Pressure-Volume Relations at End-Ejection

Reproducibility (n = 7)

	Slope		V_0		r		
Dog	Control 1	Control 2	Control 1	Control 2	Control 1	Control 2	ΔESV
1	4.0	3.6	16	14	0.99	0.99	−0.6
2	3.4	3.1	18	14	0.99	0.98	+0.6
3	2.9	2.4	39	28	0.98	0.94	0
4	5.1	5.3	19	18	0.96	0.99	+1.9*
5	5.0	4.9	1	1	0.99	0.96	+0.1
6	3.8	3.8	23	23	0.98	0.98	+0.24
7	4.6	4.1	9	4	0.97	0.94	+2.0*

Propranolol (n = 5)

	Slope		V_0		r		
Dog	Control	P	Control	P	Control	P	ΔESV
1	4.7	4.1	14	12	0.99	0.99	+1.4
2	5.2	5.6	10	14	0.97	1.00	+1.8*
3	4.2	5.2	7	14	0.98	1.00	+2.0*
4	3.2	3.3	14	17	0.99	0.98	+1.9*
5	5.2	4.5	23	20	0.98	0.99	+1.3*

Dobutamine (n = 7)

	Slope			V_0			r			ΔESV	
Dog	Control	LD	HD	Control	LD	HD	Control	LD	HD	LD	HD
1	3.1	4.7	6.2	14	21	21	0.98	0.98	0.95	−4.9*	−10.0*†
2	2.4	4.0	6.1	28	47	51	0.94	0.97	0.99	−5.6*	−15.3*†
3	5.3	6.5	8.4	18	10	11	0.99	0.97	0.99	−11.0*	−14.0*†
4	4.9	7.6	8.2	1	7	6	0.96	0.98	0.99	−2.9*	−5.4*†
5	3.8	5.0	7.0	23	23	25	0.98	1.00	0.98	−5.3*	−7.9*†
6	4.1	7.7	9.6	4	11	9	0.94	1.00	0.99	−4.8*	−9.1*†
7	8.3	10.9	19.9	4	4	6	0.99	0.96	0.98	−3.3*	−4.7*†

*$p < 0.05$ versus control, or control 2; †$p < 0.05$ versus low dose dobutamine. ΔESV = change of end-systolic volume at constant systemic pressure; HD = high dose dobutamine; LD = low dose dobutamine; P = after propranolol; r = correlation coefficient; V_0 = volume-axis intercept of the relation.

test was used to test for differences between specific means (19). Overall comparison among regression lines was accomplished by an F test, and when significance was achieved, pairwise comparisons of slopes or intercepts for displacement of the pressure-volume (and pressure-wall thickness) relations at end-ejection were made at a constant pressure (mean left ventricular pressure at end-ejection of the control relation) by the appropriate *t* test (20). Data are expressed as mean ± standard deviation unless otherwise stated.

Results

Average left ventricular hemodynamic and volume data at control and after drugs, but without angiotensin infusion, are summarized in Table 1. Representative pressure-volume and pressure-wall thickness loops obtained during angiotensin infusion are shown in Figure 1. Data on the left ventricular pressure-volume and pressure-wall thickness relations at end-systole are shown in Tables 2 and 3, respectively.

Reproducibility on the same day. Rest heart rate and maximal dP/dt were not significantly changed when studies were repeated on the same day (Table 1). End-systolic pressure-volume relations showing reproducibility (Fig. 2) illustrate the largest, least and typical differences between them. In each relation, the correlation coefficient was at least 0.94, and in each dog neither the slope nor V_o (intercept on volume axis) was changed significantly (Table 2). Slight displacement at a common pressure was significant in two dogs (Table 2). Thus, in conscious dogs at rest, end-systolic pressure-volume relations are considered to be linear and highly reproducible on the same day.

Detection of increased contractility. Low and high dose dobutamine did not significantly change the rest heart rate, but increased the systolic pressure (Table 1). Figure 3 (upper panels) and Table 2 show end-systolic pressure-volume relations during dobutamine infusions. Displacement of the

Table 3. Pressure-Wall Thickness Relations at End-Ejection

Reproducibility (same day) (n = 7)

	Slope		Th_0		r		
Dog	Control 1	Control 2	Control 1	Control 2	Control 1	Control 2	ΔESWTh
1	−38	38	16.8	16.7	−0.99	−0.97	+0.12*
2	−48	−38	18.8	19.4	−0.98	−0.998	−0.01
3	−57	−48	12.8	13.4	−0.97	−0.93	−0.08
4	−57	−51	16.4	16.7	−0.98	−0.98	−0.08
5	−31	−30	18.4	18.6	−0.98	−0.95	−0.05
6	−46	53	15.6	15.3	−0.99	−0.94	+0.05
7	−34	−30	16.1	16.7	−0.989	−0.96	−0.26*

Propranolol (n = 5)

	Slope		Th_0		r		
Dog	Control	P	Control	P	Control	P	ΔESWTh
1	−45	−47	15.2	14.9	−0.99	−0.99	−0.15*
2	−40	−48	14.2	13.5	−0.98	−0.997	−0.16
3	−50	−60	14.2	13.8	−0.98	−0.998	−0.09
4	−40	−45	19.0	8.7	−0.98	−0.98	−0.10*
5	−55	−49	16.1	16.0	−0.996	−0.98	−0.38*

Dobutamine (n = 7)

	Slope			Th_0			r			ΔESWTh	
Dog	Control	LD	HD	Control	LD	HD	Control	LD	HD	LD	HD
1	−38	−54*	−73*	19.4	18.9	18.7	−0.998	−0.98	−0.95	+0.28*	+0.67*†
2	−48	−81	−100*	13.4	12.3	12.7	−0.93	−0.98	−0.92	+0.21*	+1.05*†
3	−51	−59	−64	16.7	18.0	18.4	−0.98	−0.97	−0.995	+1.46	+2.02*†
4	30	−46*	−42	18.6	17.5	18.1	−0.95	−0.998	−0.97	+0.40*	+0.78*†
5	−53	−59	−70	15.3	15.5	15.5	−0.94	−1.000	−0.993	+0.41*	+0.68*†
6	−30	−46	−42	16.7	16.4	17.4	−0.96	−0.99	−0.98	+0.73*	+1.60*†
7	−42	−45	−63*	18.3	18.9	18.8	−0.99	−0.96	−0.99	+0.65*	+1.22*†

*$p < 0.05$ versus control; †$p < 0.05$ versus low dose dobutamine. ΔESWTh = change in end-systolic wall thickness at constant systemic pressure; HD = high dose dobutamine; LD = low dose dobutamine; P = after propranolol; r = correlation coefficient; Th_0 = dimension-axis intercept of the relation.

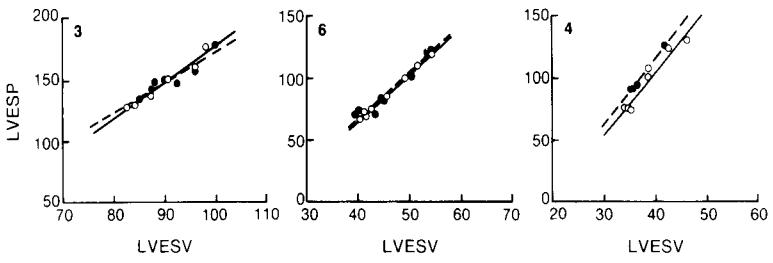


Figure 2. Representative relations between left ventricular end-systolic pressure (LVESP) and left ventricular end-systolic volume (LVESV) in seven dogs obtained by stepwise angiotensin II infusions showing reproducibility. These relations are indicative of the ranges of observed responses. The second relation (**closed circles**) obtained an average of 55 minutes later is superimposable on the first relation (**open circles**). Numbers in upper left corners refer to the number of the individual dog.

relations (that is, the calculated ventricular volumes at an average end-ejection pressure) was significant in all dogs at both low and high doses; the average end-systolic volume was significantly decreased during dobutamine infusion in all dogs, and the difference between low and high dose dobutamine was also significant in all dogs (Table 2).

In general, the slopes steepened as contractility increased, but with low dose dobutamine, the change in slope was not statistically different in two of seven dogs. In five of seven dogs, slope changes were not significant between low and high dose dobutamine, but in all dogs the slopes with high dose dobutamine were significantly steeper than control (Fig. 3). The intercept (V_0) changes were inconsistent with both doses (Table 2).

Comparison with standard indexes. With low dose dobutamine, the ejection fraction was not significantly increased at rest before angiotensin infusion, but wall stress was increased by 9% (Table 1, Fig. 4, left). During maximal angiotensin infusion, the ejection fraction with low dose dobutamine fell below the rest control value, but at wall stress values similar to those during control angiotensin infusion, the ejection fraction values were higher during inotropic stimulation. Thus, the end-systolic relations are more useful than the load-sensitive ejection fraction, unless wall stress values can be matched. With high dose dobutamine, ejection fraction values were significantly higher than control at all points, despite higher wall stress levels, so that determination of the ejection fraction was satisfactory for detecting a change when the alteration in contractility was large.

The associated changes in maximal left ventricular dP/dt are also plotted against wall stress in Figure 4 (right). Associated changes in left ventricular end-diastolic pressure

Figure 3. Upper panels, Representative relations between end-systolic pressure (LVESP) and volume (LVESV) before (**closed circles**) and after two levels of dobutamine infusion (**open triangles,** low dose dobutamine; **open circles,** high dose dobutamine). Dobutamine caused a leftward and upward shift of the linear left ventricular end-systolic pressure-volume relation and increased its slope. **Lower panels,** Representative relations between left ventricular end-systolic pressure (LVESP) and left ventricular end-systolic volume (LVESV) before (**closed circles**) and after (**open circles**) the injection of propranolol. Individual data points after propranol appeared to shift rightward and downward of the relation before, but the changes were not significant. Numbers in upper left corners of both panels refer to the number of the individual dog.

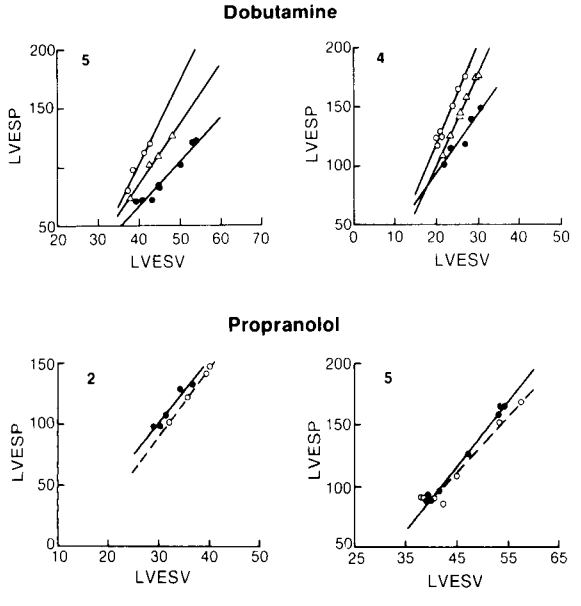
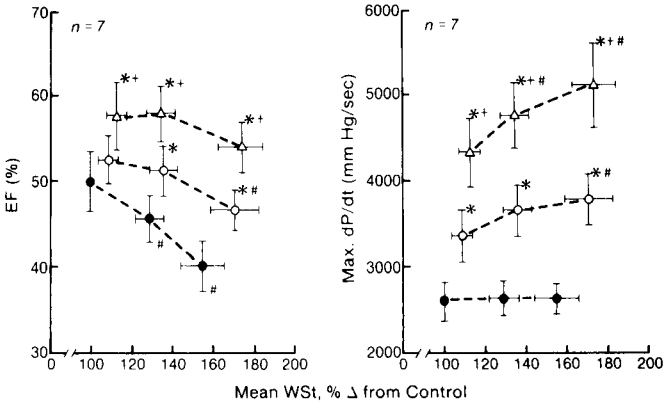


Figure 4. Effects under rest conditions and at two levels of angiotensin infusion of low and high dose dobutamine on the ejection fraction (EF) (**left panel**) and maximal first derivative of left ventricular pressure (Max. dP/dt) (**right panel**) in seven dogs. Increasing levels of mean wall stress (WSt) produced by the two doses of angiotensin are plotted as a percent of the control value. ● = control; ○ = low dose dobutamine; △ = high dose dobutamine. *, + and # = $p < 0.05$,* versus control at each wall stress level, + comparing high versus low dose dobutamine at each wall stress level and # versus before angiotensin.



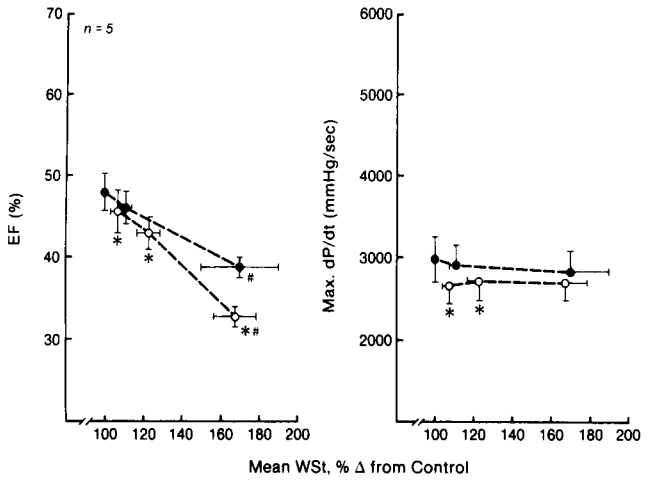


Figure 5. Effects under rest conditions and at two levels of angiotensin (AGT) infusion of propranolol on the ejection fraction (EF) (**left panel**) and the maximal first derivative of left ventricular pressure (Max. dP/dt) (**right panel**) in five dogs. Increasing levels of mean wall stress (WSt) produced by the two doses of angiotensin are plotted as a percent of the control value. ● = control; ○ = propranolol. *, # = $p < 0.05$,* versus control at each wall stress level and # versus before angiotensin.

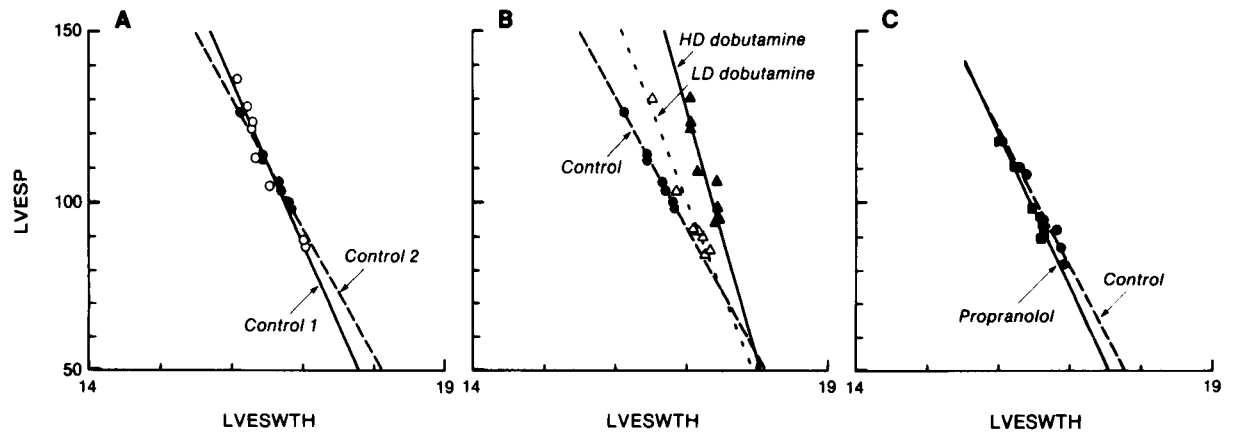
before and during angiotensin infusion were from 9 to 17 mm Hg (control), from 12 to 21 mm Hg (low dose dobutamine) and from 13 to 20 mm Hg (high dose dobutamine). Compared with control, maximal dP/dt increased more during angiotensin infusion with dobutamine, and at all points of angiotensin infusion, both with low dose and high dose dobutamine, maximal dP/dt was significantly higher than control values. Therefore, despite widely ranging preloading and afterloading conditions, end-systolic relations conferred no advantage over maximal dP/dt for detecting acute increases in contractility.

Detection of mildly depressed contractility. The infusion of propranolol (1 mg/kg) did not change the rest heart rate (Table 1). Changes in both slope and intercept on the volume axis (V_0) of the end-systolic relations were inconsistent (Table 2, Fig. 3, lower panels). There was slight displacement to the right (Fig. 3), which was significant in four of five dogs and for the group (Table 2), although the separation between pre- and post-propranolol relations was minor and similar to that observed in several of the reproducibility studies (Fig. 2).

Comparison with standard indexes. Under control conditions after propranolol, the ejection fraction was mildly but significantly decreased; however, there was a slight increase in mean wall stress (Fig. 5, left). At a matched wall stress (with low dose angiotensin), the ejection fraction was not different from control. With high dose angiotensin, ejection fraction values decreased both in the control state and after propranolol at comparable levels of wall stress, but there was a considerably more marked decrease in ejection fraction after propranolol. This indicates increased afterload sensitivity of the mildly depressed left ventricle, and suggests that under conditions of increased loading, ejection fraction may be more useful than end-systolic relations. Under normal loading conditions, both methods were marginal for detecting mild depression of contractility.

Changes in maximal left ventricular dP/dt caused by propranolol are plotted versus wall stress in Figure 5 (right). Associated changes in left ventricular end-diastolic pressure before and during angiotensin infusions were 11 to 19 mm Hg (control), and 13 to 24 mm Hg after propranolol. Maximal dP/dt decreased significantly after propranolol at low wall stress levels, but with high dose angiotensin the difference was not significant. In fact, maximal dP/dt failed to increase during angiotensin infusion after propranolol, as

Figure 6. Representative examples of relations between left ventricular end-systolic pressure (LVESP) and left ventricular end-systolic wall thickness (LVESWTH). **A**, Representative reproducibility of the relations obtained 30 minutes apart in eight dogs. **B**, Relations during a control angiotensin II infusion and after low dose (LD) and high dose (HD) dobutamine in seven dogs. **C**, Relations on a different day during control and after the injection of propranolol in five dogs.



during angiotensin infusion after dobutamine. Thus, maximal dP/dt appeared more valuable, compared with either the ejection fraction or end-systolic measures, for detecting small decreases in contractility when loading conditions remained relatively constant.

Pressure-wall thickness relations at end-ejection. Representative left ventricular pressure-wall thickness loops are shown in Figure 1B, and data on left ventricular pressure-wall thickness relations at end-systole are presented in Table 3. In all dogs, the end-systolic pressure-wall thickness relations were linear with high correlation coefficients (Fig. 6). They were also reproducible, with no consistent or significant changes in slope or intercept; only two of seven dogs showed slight but significant displacement of wall thickness at a common pressure.

During low and high dose dobutamine, the slopes became steeper in all dogs, but the changes were statistically significant in only three of seven dogs. As a group, the differences in slopes and intercepts between low and high dose dobutamine were not statistically significant. However, the calculated wall thickness at the average end-ejection pressure of the control angiotensin infusion showed significant rightward displacement during both low and high dose dobutamine infusions in all seven dogs (Table 3, Fig. 6). The difference between low dose and high dose dobutamine was also statistically significant in all seven dogs (Table 2). Thus, displacement of the end-systolic pressure-wall thickness relation detected increases in contractility, whereas the change in slope was less reliable.

During the mildly depressed contractile state produced by propranolol, the slopes and intercepts of the relation on the wall thickness axis were not significantly changed (Table 3, Fig. 6). There was displacement in three of five dogs, but the average shift was not significant. These findings resembled those using end-systolic pressure-volume relations and indicate insensitivity to mild contractility depression.

Discussion

Using normal conscious dogs and a two point analysis of pressure loading with phenylephrine, Mahler et al. (4) demonstrated that the left ventricular end-systolic pressure-diameter relation was shifted leftward by positive inotropic stimulation induced by digoxin or isoproterenol; it was not affected by changes in preload, confirming the usefulness of end-systolic pressure-diameter relations in the intact animal heart for defining contractility. For characterizing the contractile state of the human left ventricle, Grossman et al. (7) measured the left ventricular or aortic pressure simultaneously during left ventricular cineangiography before and 15 minutes after the start of an intravenous infusion of sodium nitroprusside. From these data, they reported that the slope of the resultant relation was significantly steeper for the normal than for the poorly contractile left ventricle and that the volume axis intercept of the line was significantly smaller. However, as in the study of Mahler et al. (4), the limited number of measurement points (two) did not allow documentation of the linearity of the relations or their sensitivity for detecting depressed contractility. Mehmel et al. (11) performed three ventriculograms and also analyzed postextrasystolic beats in patients, and reported that end-systolic pressure-volume points were linear under control conditions, with displacement of the lines toward the left in postextrasystolic beats. Linearity was also reported by other investigators (8–10,12) using echocardiography for the measurements of left ventricular dimension or volume, and in other studies (6,21) vena caval obstruction in conscious instrumented dogs was employed to generate linear end-systolic pressure-volume or pressure-diameter relations that exhibited increases in slope with inotropic stimulation. Although end-systolic pressure-volume (or diameter) relations are now used as a means of defining contractile state in the intact heart, the advantage of using wall stress instead of pressure to correct for the effect of chronic ventricular muscle hypertrophy has been noted (5,10,22).

Reproducibility and sensitivity of end-systolic relations. None of the previous studies has analyzed the reproducibility of these relations to sequential vasopressor infusions in the intact circulation or their sensitivity for detecting changes in individual relations. In this study, we used a method described previously (15,17) and shown to be reliable for repeated measurements of left ventricular volume. Although the infusion of angiotensin at very high doses might have changed myocardial contractility (23), it seems unlikely that angiotensin at the infusion rates (≤ 2.0 μg/min) in this study had such a direct effect, and this pressure agent has previously been shown to be useful in humans (16).

The present study confirmed the excellent linearity of the relation between left ventricular pressure and volume at end-systole over a physiologic range of afterloading conditions in the conscious dog at rest without heart rate control. We also showed that the relation was highly reproducible when angiotensin infusion was repeated. The slopes of end-systolic pressure-volume relations increased during low dose dobutamine; changes in volume axis intercept were inconsistent, but the calculated left ventricular end-systolic volume at the average end-ejection pressure of the control angiotensin infusion was clearly displaced to the left at both levels of increased myocardial contractility. Because our actual measurements were done at a level far from the zero pressure intercept on the volume axis, inherent noise is emphasized by extrapolation to the volume axis and, therefore, we sought an approach to demonstrate displacement

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of relations within a physiologic pressure range. It seemed reasonable, therefore, to analyze this calculated volume at an average pressure in addition to the volume intercept for demonstrating shifts of the relation. Therefore, end-systolic pressure-volume relations provide a reproducible and load-independent means of identifying increases in left ventricular contractility in individual conscious animals.

Determination of the left ventricular end-systolic pressure-volume or pressure-diameter relations, of course, requires a reliable method for altering loading conditions, as well as multiple determinations of left ventricular volume and pressure. Therefore, their application is somewhat limited. On the other hand, it is possible to determine pressure-dimension relations noninvasively (10), and the end-systolic pressure-wall thickness relation that we describe could also be so determined. However, when afterloading conditions do not change appreciably, the ejection fraction or fractional shortening is simpler to determine and provides a reliable measure of contractility (24) as shown also in this study. In addition, it is highly useful for assessing inotropic state under basal conditions in human disease (25).

Comparison of end-systolic relations with standard contractility indexes. When invasive studies are done to assess acute changes in contractility, as we have demonstrated, it may not be necessary to determine end-systolic relations because maximal left ventricular dP/dt alone could detect acute increases and decreases in contractility, regardless of the loading conditions studied in this conscious animal preparation. The measure is mildly sensitive to preload changes in the intact animal, as previously shown (24), and this study suggests that maximal dP/dt shows increasing preload sensitivity with progressive enhancement of inotropic state (Fig. 4). Also, the possibility cannot be excluded that an additional inotropic effect due to angiotensin occurred in the presence of dobutamine. Nevertheless, such effects did not appear to impair the usefulness of maximal dP/dt for identifying acute increases in contractility in the animal model. It should be emphasized that these inclusions apply only to the range of pressures studied, and might not apply under more extreme loading conditions. Also, they apply to the setting of acute interventions, and it is likely that end-systolic relations, including considerations of wall stress, are more useful when there are chronic changes in loading conditions or contractility (22). Finally, maximal dP/dt alone may change relatively little with moderate acute regional ischemia; end-systolic relations or the ejection fraction might be more useful than left ventricular dP/dt in this setting, and regional end-systolic pressure-wall thickness relations were shown to detect depressed regional contractility during acute ischemia (13).

The slopes of the end-systolic pressure-volume relations and the volume intercepts failed to detect a mild decrease in contractility induced by propranolol in all dogs, whereas the decrease in maximal dP/dt ($-11 \pm 6\%$) was significant, suggesting the standard indexes may be superior to end-systolic relations for detecting slight acute depression in contractility. Sympathetic tone has been shown to be low in the normal conscious animal (26), and the changes in ejection fraction in response to increased afterload in this study support the presence of a mildly depressed contractile state with increased afterload sensitivity (Fig. 5). Thus, under conditions of elevated afterload, the ejection fraction detected an acute mild decrease in contractility.

Mehmel et al. (11) reported on the correlation between the ejection fraction, determined from left ventriculograms, and the slopes of end-systolic pressure-volume relations; the resulting exponential plot was fairly steep at ejection fraction values above 50%, but shallow at ejection fraction values less than 50%. Their results appear to agree with ours, suggesting less sensitivity of the end-systolic pressure-volume relation to depressed contractility than to enhanced inotropic state (although in our study, the relative changes in contractility produced by propranolol were smaller than with low dose dobutamine).

End-systolic pressure-wall thickness relations. We also examined the potential usefulness of left ventricular end-systolic pressure-wall thickness relations for characterizing contractile state. Osakada et al. (13) demonstrated the applicability of end-systolic pressure-wall thickness relations for defining the regional contractile state of left ventricular myocardium by creating partial to complete inferior vena cava occlusion in conscious dogs. Miller et al. (14), using anesthetized pigs, reported that a regional elastance variable (the end-systolic pressure-segment length relation) was shifted only after treatment with dobutamine (5 to 13 μg/mg per min), whereas changes in the global index (the end-systolic pressure-diameter relation) occurred both during enhanced contractility and during depressed myocardial contractile state produced by propranolol (6 to 51 μg/kg per min). In this study, we observed linearity and reproducibility of the regional relations, which were comparable with those of end-systolic pressure-volume relations. Although the slopes of end-systolic pressure-wall thickness relations steepened in some experiments (Fig. 6) with low and high dose dobutamine, they did not change consistently; however, the end-systolic pressure-wall thickness points were progressively and consistently displaced to the right with enhanced contractility. The effect of propranolol was inconsistent, being comparable with the findings using end-systolic pressure-volume relations. It is possible that the finding with propranolol by Miller et al. (14), which differs from that in our study, is related to the higher level of sympathetic tone present in the anesthetized animal in their study. Use of the end-systolic pressure-wall thickness relation, which could be determined echocardiographically, does not require calculation of left ventricular volume and, in the absence of

regional wall motion abnormalities, it could provide a simplified load-independent means of assessing changes in global contractility of the left ventricle in the intact state.

Limitations of study. Several potential limitations of our methods should be considered. First, the left ventricular volume calculation was based on ventricular dimensions measured by sonomicrometry. The calculated volume was shown to correlate well with changes in measured volume (15), but it was not identical. This potential source of error may be in part responsible for the somewhat different results from previous studies in anesthetized dogs (1–3) in which the left ventricular volume was measured precisely; in our study, the end-systolic pressure-volume relation rarely extrapolated to zero on the volume axis. However, such an error should not appreciably affect the ability to detect shifts in the relations.

Angiotensin could have had some effect on myocardial contractility. However, Downing and Sonnenblick (23) demonstrated that the doses of angiotensin that we used had no effect on contractility. Tajimi et al. (27) failed to find an enhanced contractile state after angiotensin infusion (0.6 to 0.8 μg/min), whereas they reported a positive inotropic action due to the beta-adrenergic action of phenylephrine infusion (20 to 25 μg/min), a problem not observed with the relatively pure alpha$_1$ agonist methoxamine.

Sodums et al. (21) reported that increases in afterload produced by angiotensin infusion resulted in a parallel shift of the end-systolic pressure-volume relation compared with that obtained by occlusion of the inferior vena cava; this shift was independent of the level of inotropic state. Further, Maughan et al. (28) reported the potential dependence of the volume-axis intercept on resistance and characteristic impedance. The cause of these shifts is unclear. Nevertheless, in this study, we demonstrated that linear and reproducible end-systolic pressure-volume (and wall thickness) relations can be obtained by angiotensin infusion, and that these relations were shifted by acute increases in contractility. Moreover, the use of vena caval occlusion is a difficult technique to apply in humans. Thus, it appears that production of changes in afterloading conditions by angiotensin infusion is applicable in the intact animal, and it may be similarly useful in humans as well.

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