Interrelation between end-systolic pressure-volume and pressure-wall thickness relations

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SCHIPKE, JOCHEN D., JOE ALEXANDER, JR., YASUHIKO HARASAWA, RAINER SCHULZ, AND DANIEL BURKHOFF. *Interrelation between end-systolic pressure-volume and pressure-wall thickness relations.* Am. J. Physiol. 255 (Heart Circ. Physiol. 24): H679–H684, 1988.—We predicted the shape of the end-systolic pressure-thickness relationship (ESPTR) by modeling the left ventricle as thick-walled sphere. To test the validity of the predicted relationships, we then measured the ESPTR over wide volume ranges in seven isolated blood-perfused canine hearts. Both simulation and experiments demonstrated that the ESPTR is curvilinear. However, within a physiological left ventricular systolic pressure range (80–150 mmHg), the ESPTR was described reasonably well by a straight line. Within that pressure range, changes in left ventricular contractile state, assessed by slope changes of the end-systolic pressure-volume relationship, were associated with almost parallel shifts in the ESPTR. In contrast, in a low pressure range (<80 mmHg), contractility changes were associated with slope changes of the ESPTR. We conclude that, in general, there are limitations in the application of ESPTR for assessing left ventricular contractility, but if the limitations are recognized and accounted for, then the ESPTR may be useful for assessing contractility changes in vivo.

canine left ventricle; contractility; ultrasonic measurement

THE CONCEPT OF USING THE SLOPE of the end-systolic pressure-volume relation (ESPVR) as an index of ventricular contractile state is relatively old (5). Although the relationship has been shown to provide valuable insight into ventricular systolic function (6, 11, 15), its application to the heart remains limited because an easy measurement of instantaneous ventricular volume is not routinely available. To circumvent this difficulty, several investigators attempted to substitute global or regional ventricular dimension signals for ventricular volume. One such dimensional signal is wall thickness, and the characteristics of the end-systolic pressure-thickness relationship (ESPTR) have been studied extensively (1, 7, 12). In contrast to the ESPVR, the ESPTR can also provide information about regional contractile function in a heart that has inhomogeneous myocardial properties. The effects of altered contractility on ESPTR vary from one report to another. Osakada and colleagues (10) found the ESPTR to be linear and shift rightward with enhanced myocardial contractility and leftward with reduced contractility. Lee et al. (7) also obtained linear ESPTRs and stated that a horizontal shift of the ESPTR was a more reliable sign of change in contractility than a change in the slope of this relation. In contrast, Aversano et al. (1) described that increases in contractility were associated with increased slope of the ESPTR, whereas decreases in contractility induced a parallel leftward shift. Other studies in open-chest dogs (12) and humans (2) reported, however, changes in the slope of the ESPTR with both positive and negative changes in contractile state.

The objective of this study was to try to explain these disparate results through analysis of a simple model and further experimental work. In the first phase of this study we examined the theoretical ESPTR of a model ventricle with spherical geometry. The model yielded a nonlinear ESPTR. This suggested to us that the variable results cited above might derive from limited ranges over which changes in pressure and wall thickness were measured in those studies. Therefore, in the second phase of our study we measured the ESPTR in isolated canine hearts over a wide range of pressure and wall thickness and determined the influence of inotropic interventions on the ESPTR.

METHODS

Ventricular Model Analysis

In modeling the ventricle, we assumed that it is composed of incompressible material, and we will consider only the properties at a single point in time, namely, end systole. The relation between end-systolic wall thickness (WT_{es}) and end-systolic volume (V_{es}) for a sphere is expressed by

$$WT_{es} = \sqrt[3]{3/(4\pi)} \left(\sqrt[3]{V_w + V_{es}} - \sqrt[3]{V_{es}} \right) \qquad (1)$$

where V_w is the volume of the ventricular wall. The relationship between end-systolic pressure (P_{es}) and V_{es} in canine ventricles can be approximated by a linear equation within the physiological range of pressures and contractile state (3)

$$P_{es} = E_{es}(V_{es} - V_0) \qquad (2)$$

where E_{es}, an index of contractility, is the slope and V_0 is the volume-axis intercept of the ESPVR. When *Eqs.*

1 and *2* are combined, we obtain the following equation from which the ESPTR can be calculated

$$WT_{es} = \sqrt[3]{3/(4\pi)} \left(\sqrt[3]{V_w + P_{es}/E_{es} + V_0} - \sqrt[3]{P_{es}/E_{es} + V_0} \right) \quad (3)$$

Burkhoff et al. (3) showed that, when large changes in contractile state and volume are made, the ESPVR could become curvilinear (3). Then the general formula for the ESPVR is

$$P_{es} = aV_{es}^2 + bV_{es} + c \quad (4)$$

where *a*, *b*, and *c* are variables. In this curvilinear case, the authors proposed to index contractility by the slope of the ESPVR in the low volume range (E'_{es}). This index is defined mathematically as

$$E'_{es} = \sqrt{b^2 - 4ac} \quad (5)$$

The extent of curvilinearity in the ESPVRs was shown to be a function of E'_{es}. When *Eqs. 4* and *1* are combined, we obtain the following equation which defines the ESPTR

$$WT_{es} = \sqrt[3]{3/(4\pi)} \left(\sqrt[3]{V_w - (b/2a) \pm \sqrt{b^2/4a^2 - (c - P_{es})/a}} - \sqrt[3]{-(b/2a) \pm \sqrt{b^2/4a^2 - (c - P_{es})/a}} \right) \quad (6)$$

Isolated Ventricular Preparation

General preparation. The details of the isolated blood-perfused canine heart preparation have been previously described (14). Briefly, a pair of mongrel dogs (20–25 kg) was anesthetized with pentobarbital sodium (30 mg/kg iv). The heart was removed from one dog (donor dog) and perfused with blood from the second dog (support dog) using a constant-pressure perfusion pump. Mean coronary arterial pressure was monitored (Statham, P23 Db) via a cannula in the brachiocephalic artery. After opening the left atrium and cutting the chordae tendineae, a thin-walled latex balloon (connected to a servo-controlled pump) was fitted in the left ventricular cavity. The space between the balloon and the ventricular wall was vented as was the right ventricular cavity. A constant volume of water filled the pump and the balloon. Thus absolute volume changes in the balloon could be controlled accurately and measured by the volume servo-pump. Left ventricular pressure was measured with a catheter-tip manometer (Millar, PC-380).

The ventricular wall thickness was measured by a sonomicrometer (Triton Technology, model 120). The internal crystal was positioned between the intracavitary balloon and the endocardium without using any suture. The crystal was attached to a piece of umbilical tape that entered the ventricle at the base and exited from the apex. The crystal position could be adjusted by pulling the tape in either the basal or the apical direction. The external crystal was carefully sutured at the epicardial equator at a point that optimized the signal and minimized the transit time. In this way, the attachment of the crystals was almost free of myocardial injury.

Left ventricular pressure, ventricular volume, myocardial wall thickness, coronary arterial pressure, and support dog arterial pressure were recorded continuously on a chart recorder (Gould, model 2800). The data were digitized at a rate of 200 Hz (12-bit analog-digital converter) and stored on magnetic disk for off-line analysis.

Experimental Protocol

Experiments were performed on seven canine hearts that were ejecting against a simulated arterial afterload system (16). The ventricles were paced at 20% above their spontaneous rate. The coronary arterial pressure was kept constant at 20% below the left ventricular peak systolic pressure at the control volume (29.3 ± 5.3 ml). After a steady-state condition was reached at a high end-diastolic volume, the ventricular volume was steadily decreased using the servo-system to obtain the ESPVR and the ESPTR. This protocol was then repeated after *1*) infusion of 0.5 μg/min dobutamine into the coronary perfusion line and *2*) administration of 1 mg propranolol into the coronary perfusion line.

For simplicity, the end of systole was defined as end ejection.

RESULTS

Model Analysis

The ESPTR was simulated for linear and nonlinear ESPVR with variable contractilities. E_{es} of the linear ESPVR was varied over a range between 3 and 9 mmHg/ml, with a constant V_0 of 2.5 ml (Fig. 1*A*). These relationships were transformed into ESPTRs via the thick-walled sphere model (*Eq. 3*) as shown in Fig. 1*B*. Ventricular mass was assumed to be 120 ml. The family of ESPTRs exhibited a curvilinearity that became more pronounced at low contractile states and at low end-systolic pressures. The family of curves converged into one wall thickness-axis intercept (T_0) that corresponded to the volume-axis intercept (V_0) in the pressure-volume plane. Within a physiological end-systolic pressure range (80–150 mmHg), the curves could be considered quasi-linear, and changes in the contractile state were associated with quasiparallel shifts.

A similar simulation was executed with the nonlinear ESPVRs (Fig. 2*A*) with E'_{es} varied between 3 and 9 mmHg/ml using *Eq. 6*. Convexity of the ESPVRs toward the volume axis at low contractile states amplified the curvilinearity of the ESPTRs, whereas concavity of the ESPVRs toward the volume axis at high contractile states attenuated curvilinearity of the ESPTRs (Fig. 2*B*).

Experimental ESPTRs

ESPVRs obtained from one ventricle are shown in Fig. 3*A*. The ESPVR under control and increased (by dobutamine) contractile states were reasonably linear. Administration of propranolol decreased the contractility, and the ESPVR became convex to the volume axis. The corresponding ESPTR data are shown in Fig. 3*B*. As predicted by the model, all the ESPTRs exhibited non-

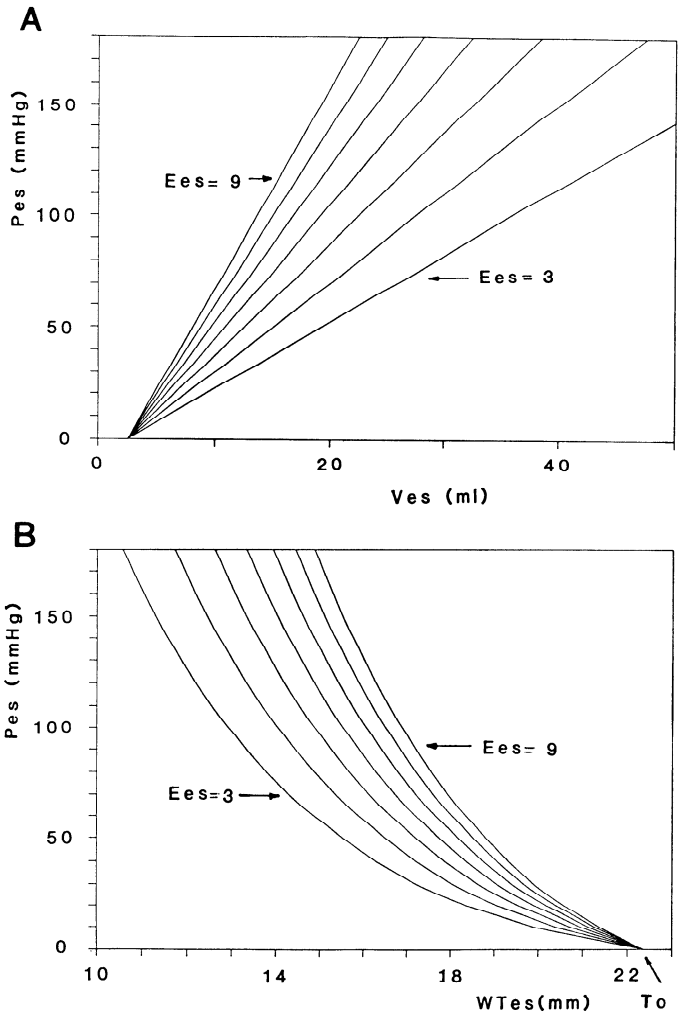

FIG. 1. Linear end-systolic pressure-volume relationships (ESPVRs) (*A*) and corresponding end-systolic pressure-thickness relationships (ESPTRs) (*B*) simulated by a sphere as a ventricular model. Family of ESPTRs is nonlinear with a tendency to higher nonlinearity at low systolic pressures and low contractile states. Within a physiological pressure range, i.e., between 80 and 150 mmHg, ESPTRs can be regarded quasilinear, and shifts in this pressure range can be used for analyzing changes in contractile state. P_{es}, left ventricular end-systolic pressure; V_{es}, left ventricular end-systolic volume; WT_{es}, left ventricular end-systolic wall thickness; E_{es}, slope of linear ESPVR (in mmHg/ml); T_0, wall thickness intercept.

linearities. Accordingly, the nature of changes in these ESPTRs with contractility depended on the range of pressures examined. In the higher pressure range, i.e., roughly in the top half of each curve, the ESPTRs were reasonably linear. Their shifts with contractility were almost parallel. In a lower pressure range, however, changes in contractility appear to affect the slope of the ESPTRs.

Data from the remaining six experiments are shown in Fig. 4. In general, the ESPVRs were reasonably linear under control conditions and tended to be concave to the volume axis at enhanced contractile states and convex to the volume axis at depressed contractile states. The ESPTRs were generally curvilinear at all levels of contractility in a manner predicted by the model. However, the extent of curvilinearity varied from one heart to the next. When contractility was enhanced, almost all the ESPTRs (except that of *heart A*) showed primarily a parallel shift to the right within a physiological range of pressures (80–150 mmHg). When contractility was decreased, three ventricles (A, C, D) could not generate physiological pressures even at high volumes, and the changes in the ESPTR from the control ESPTR were predominantly slope changes. However, in those hearts in which propranolol had a milder effect and peak ventricular pressure was >80 mmHg (B, E, F and Fig. 4), changes in the ESPTRs from control were predominantly parallel shifts.

Thus changes in contractile state can be described either as parallel horizontal displacement or as slope changes, depending on which part of the curves are analyzed. However, both theoretical and experimental end-systolic pressure-wall thickness curves show a trend of primarily parallel shifts in physiological pressure range. We therefore examined how the changes in contractility effected changes in thickness at a fixed phys-

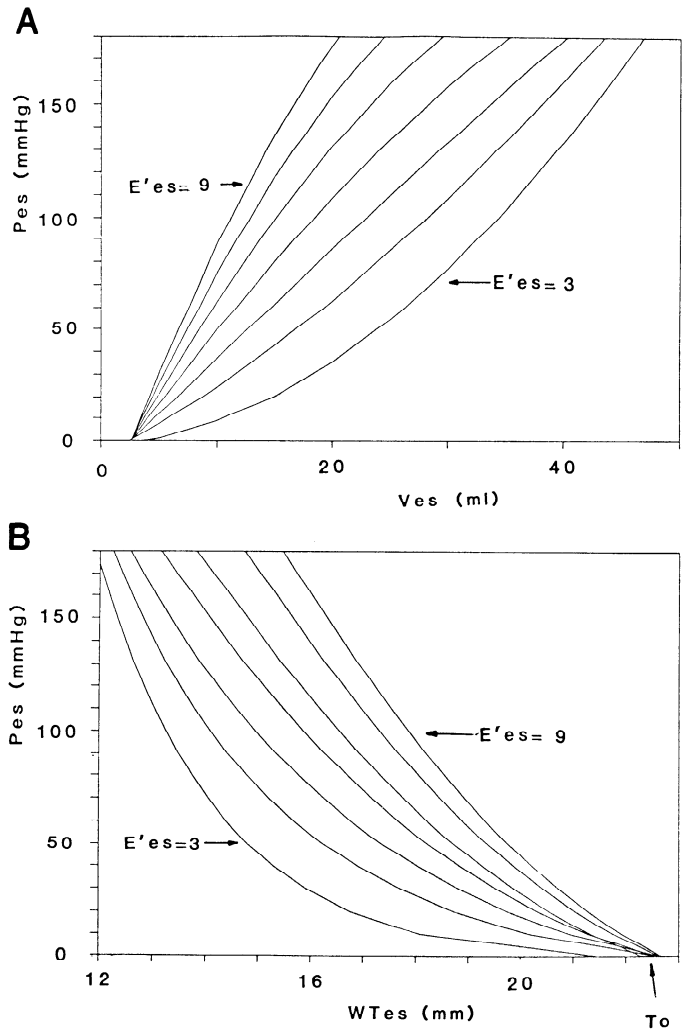

FIG. 2. Curvilinear ESPVRs (*A*) and corresponding ESPTRs (*B*) simulated by a sphere model. Curvilinearity in pressure-volume plane at low contractile states becomes amplified in pressure-wall thickness plane, and curvilinearity at high contractile states becomes attenuated. Thus changes in contractile state in terms of slope changes of ESPVR cannot reasonably be explained with parallel shifts or rotations around a common wall thickness intercept of ESPTRs. E'_{es}, slope of curvilinear end-systolic pressure-volume relationship at $P_{es} = 0$ mmHg (in mmHg/ml). See Fig. 1 for other abbreviations.

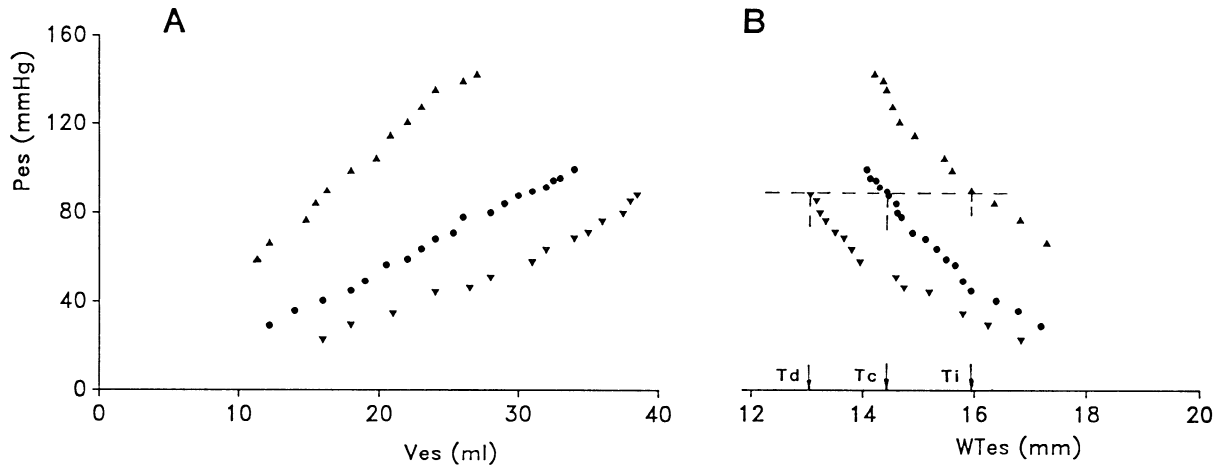

FIG. 3. Representative end-systolic pressure-volume and wall thickness-volume relations measured in a dog's heart during control conditions (●) and during increased (▲) and decreased (▼) contractile state. ESPVRs (*A*) are linear except for low contractile state after propranolol and converge into a common volume intercept (V_0 = 2.5 ml). All ESPTRs (*B*) are characterized by a distinct curvilinearity. In higher pressure range of each contractile state, ESPTRs could be regarded quasi-parallel. Wall thicknesses at an end-systolic pressure of 90 mmHg are given to index the contractile state (T_d = 13.1 mm, T_c = 14.3 mm, and T_i = 15.9 mm). See Fig. 1 for other abbreviations.

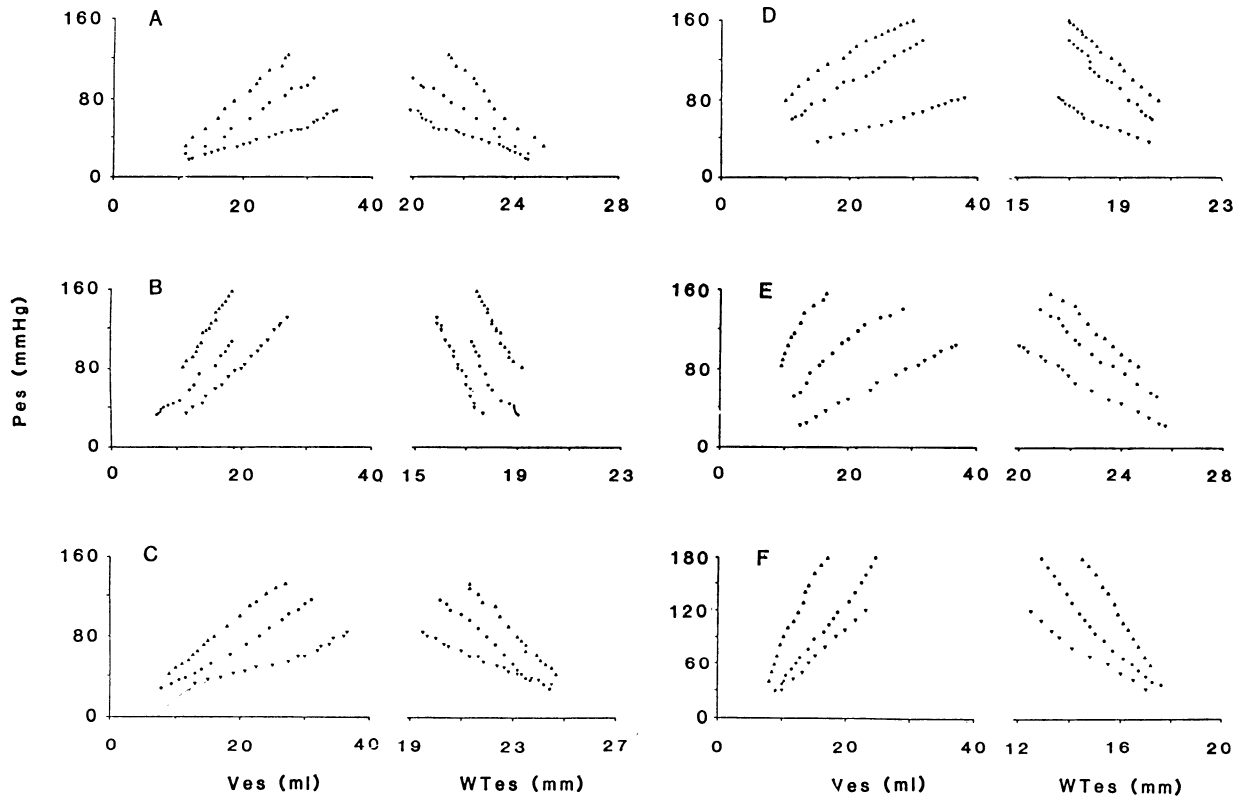

FIG. 4. ESPVRs and corresponding ESPTRs of 6 experiments (*A–F*). Extent of nonlinearity of ESPTRs varied from one heart to the other and generally was more pronounced at low contractile states and low pressures. See Fig. 1 for other abbreviations.

iological level of end-systolic pressure. An example is shown in Fig. 3*B*, where an end-systolic pressure of 90 mmHg was selected as the "reference" pressure. As shown, the end-systolic wall thicknesses for the control (T_c), increased (T_i) and decreased (T_d) contractile states at this end-systolic pressure were $T90_c$ = 14.3, $T90_i$ = 15.9, and $T90_d$ = 13.1 mm, respectively.

Data from all seven hearts are summarized in Table 1. To quantify changes in contractility, we calculated the E_{es}, making the assumption that the ESPVRs were linear. On average, administration of propranolol decreased E_{es} by 31 ± 17% (means ± SD), and during infusion of dobutamine the slope increased by 47 ± 22%. The corresponding thickness values at 90 mmHg in all the ventricles are also listed in Table 1. For those ventricles in which an end-systolic pressure of 90 mmHg was not attained, T90 was estimated by linear extrapolation from the points obtained above 60 mmHg (indicated by an

TABLE 1. *Slope of end-systolic pressure-volume relation and the left ventricular wall thickness at an end-systolic pressure of 90 mmHg during control, after administration of propranolol, and during infusion of dobutamine*

Group	Control		Propranolol (1 mg)				Dobutamine (0.5 μg/min)			
	E_{es}	T90	E_{es}	$-\Delta E_{es}$	T90	$-\Delta$T90	E_{es}	$+\Delta E_{es}$	T90	$+\Delta$T90
1	6.3	17.5	6.2	0	16.8	4	10.5	68	18.8	7
2	4.0	20.7	2.1	48	19.2*	7	5.6	39	22.5	8
3	3.9	21.6	2.1	46	19.2*	11	5.2	34	22.8	6
4	3.3	14.3	2.8	16	13.1	9	5.5	68	15.9	11
5	3.8	19.1	2.0	47	16.1*	16	3.9	3	19.9	5
6	5.3	15.3	3.4	35	13.7	11	8.1	53	16.5	8
7	9.3	23.2	6.8	27	20.9	10	15.5	67	24.4	5
Mean ± SD	5.1±2.0	18.8±3.0	3.6±1.9	31±17	17.0±2.7	10±3	7.8±3.8	47±22	20.1±3.0	7±2

Values that are changing (Δ) are relative changes of slope of end-systolic pressure-volume relation (E_{es}) and left ventricular wall thickness at end-systolic pressure of 90 mmHg (T90) from control. E_{es} measured in mmHg/ml; Δ measured in %; T90 measured in mm. * Extrapolated to an end-systolic pressure of 90 mmHg.

asterisk in Table 1). An average leftward shift of 10 ± 3% occurred after administration of propranolol, whereas infusion of dobutamine induced a rightward shift of 7 ± 2%. The percent changes in the ESPTRs measured in this way were less sensitive than changes in the ESPVRs measured in terms of E_{es}.

DISCUSSION

Analysis of a simple sphere model of the ventricle shows a clear curvilinearity of the ESPTR independent of whether linear or curvilinear ESPVRs were used. Experiments performed on isolated blood-perfused canine hearts, which permitted the simultaneous and accurate measurement of both intraventricular volume and wall thickness, support these simulation results. This curvilinearity has not been clearly demonstrated previously because decreases in systolic pressures in situ are usually limited to a relatively narrow range, which is insufficient to reveal the significantly curved part of the ESPTR. Thus the changes in the ESPTR with contractility depend on the pressure range of interest; in the low pressure range changes are best described as changes in slope of the ESPTR, whereas in the higher (physiological) pressure range the changes were better described as parallel shifts.

Changes in end-systolic pressure achievable in vivo for measuring the ESPTR are generally small and fall into a range in which we observed a reasonably linear ESPTR and in which contractile state changes created parallel shifts in the ESPTR. Two methods, both based on the assumption of parallel shifting ESPTRs, have been proposed previously for quantifying changes in contractility. In one method, the T_0 of the ESPTR is estimated by linear extrapolation of the data by regression analysis, and shifts of this extrapolated axis-intercept are used to quantify contractility changes (1, 7). In the second method, shift in the ESPTR are quantified by changes in the intersection of the ESPTR with a specified physiological pressure level (e.g., at 90 mmHg), in which case there is no extrapolation outside of the range of data collected (1, 4). As can be seen from our experimental data, even within the narrow physiological pressure range achievable in vivo, the ESPTR may not be truly linear and shifts of the ESPTRs may not be truly parallel. Consequently, misleading results may be obtained if the first method is used in which extrapolated T_0 is used for indexing contractility, and our data would support the second method using T90.

Comparison of our experimental data on relative changes in the measures of contractility demonstrated [in agreement with a previous study on humans (2)] that the slope of the ESPVR responded more sensitively to inotropic interventions than did horizontal shifts of the ESPTR at 90 mmHg (Table 1, ΔE_{es} = +47 and −31% vs. ΔT90 = +7 and −10%). This result is predicted by *Eq. 1*, which ascribes a nonlinear coupling between wall thickness and intraventricular volume and predicts smaller changes (i.e., lower sensitivity) in one dimensional wall thickness than in volume.

In situ measurement of the ESPTR is associated with changes in coronary arterial pressure that are known to influence wall thickness. Miller et al. (9) recently reported that changes in coronary arterial pressure from 100 to 155 mmHg were accompanied by 3% changes in wall thickness. This amount is relatively high when compared with overall changes in wall thickness. During the volume changes in our experiments, we kept the coronary arterial pressure constant. Therefore, our results are free from such perturbations, but they should be considered when interpreting in situ data.

Our wall thickness measurements were large compared with those generally obtained in situ. Several factors likely contribute to this discrepancy. First, it is likely that the isolated heart is slightly edematous when compared with in situ conditions. Second, in contrast to in situ studies that usually employ a subendocardially placed crystal, we used a crystal which was placed on the endocardium; this may add a few (1 or 2) millimeters compared with what one is used to in intact hearts just because of difference in placement and another millimeter or so due to the effects of endocardial trabeculation. Additionally, we cannot exclude the possibility that there was crystal misalignment or that the endocardial crystal was placed at the base of a papillary muscle. These factors may have influenced the shapes of the ESPTRs we measured.

In conclusion, the ESPTR measured over a wide pressure range is curvilinear. When a physiological pressure

range is investigated, theoretical and experimental results indicate that the curves can be considered quasilinear. Within that same pressure range, changes in contractility create a roughly parallel shift in the ESPTR. The use of a linearly extrapolated T_0 for assessing changes in contractility may not be as reliable as shifts in the ESPTR at a specified pressure level (e.g., T90).

We are indebted to Dr. K. Sagawa for his support of this study and review of this manuscript with helpful suggestions. We also acknowledge Dr. P. A. Murray for providing ultrasonic crystals, K. Rent for excellent technical assistance, and G. King and C. Thomalla for careful secretarial assistance.

This work was supported in part by National Heart, Lung, and Blood Institute Grant HL-18912. J. D. Schipke was supported in part by a postdoctoral fellowship from the American Heart Association, Maryland Affiliate and by the German Research Foundation (DFG; Schi 201/1-1).

Received 7 April 1988; accepted in final form 14 June 1988.

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