

## Left Ventricular Volume in Man Measured by Thermodilution \*

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The most important contributions to the quantification of left ventricular volume in man to date have employed the angiographic technic (1-3). Although stated to be accurate, this method is time-consuming, requires expensive equipment, alters ventricular contraction, is relatively limited in the number of observations that can be made safely, and may present the hazard of myocardial injury. The indicator dilution method for estimation of ventricular volume (4, 5), on the other hand, although more dependent on uniform ventricular mixing and totally unrevealing of ventricular shape, presents the advantages of having little effect on the heart, unlimited repeatability, and simplicity of calculation. This communication reports measurement of left ventricular volume in man by the thermodilution technic (6) under a variety of conditions and the utilization of these data to determine ventricular systolic force and fiber shortening.

### Methods

Thirty-nine patients were studied and classified on the basis of clinical evidence and diagnostic cardiac catheterization. Subjects with mitral regurgitation and significant aortic regurgitation were not included because of the inability to calculate true left ventricular volume in the presence of these defects (7). The following categories were studied:

"Normal" left ventricle (22 subjects). This category was divided into groups A and B according to the apparent degree of "normality." Group A comprised seven

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patients with systolic murmurs and no discernible abnormality on diagnostic catheterization and five patients with trivial mitral stenosis. Group B was composed of four with significant mitral stenosis, three with slight and two with moderate aortic stenosis (pressure gradients no higher than 30 mm Hg), and one with a surgically proved secundum-type atrial defect. No patient had cardiac enlargement by X ray or left ventricular hypertrophy by electrocardiogram (8).

*Aortic stenosis.* Eleven patients had severe aortic stenosis (calculated area of 0.6 cm<sup>2</sup> or less), confirmed at subsequent operation or necropsy in eight. Nine of these had clinical symptoms of left ventricular failure. These patients showed varying degrees of cardiac enlargement by X ray (9).

*Congestive failure of unknown etiology.* Three subjects had symptoms and signs of left ventricular failure. All had an increase in cardiac silhouette (9).

*Subaortic stenosis.* There were two subjects with hemodynamic and cineangiographic documentation of subvalvular muscular obstruction. Both were virtually free of symptoms. Radiographic heart size was normal in both. Left ventricular hypertrophy was present in both by electrocardiogram.

*Paroxysmal atrial tachycardia.* One patient with essential hypertension and a history of palpitations spontaneously went into this arrhythmia subsequent to control observations. Measurements were made just before termination of the arrhythmia by carotid sinus pressure.

*Procedure.* Catheters were placed in the left ventricle usually by the transseptal, but occasionally by the retrograde technic,<sup>1</sup> in the ascending aorta, a brachial artery, and a peripheral vein. A beaded thermistor<sup>2</sup> mounted on a radiopaque no. 4 vinyl catheter was threaded through the aortic catheter to protrude several millimeters into the blood stream immediately above the aortic valve. The thermistor was connected across a Wheatstone bridge, thence to a recording circuit. Details of this system and the methods used are described elsewhere (7).

<sup>1</sup> Cineangiographic studies in the dog have not shown visually detectable aortic insufficiency when a soft thin catheter (o.d., 0.063 inch) is placed across the aortic valve.

<sup>2</sup> 32A50, Victory Engineering Company, Union, N. J.

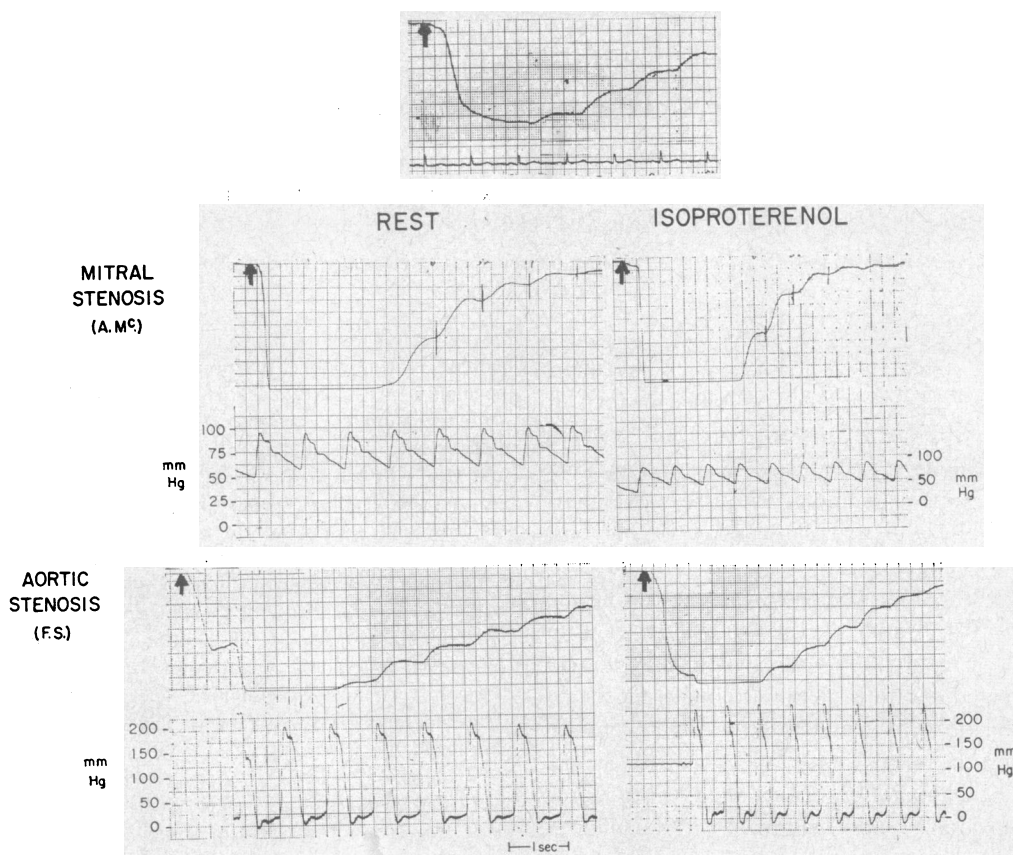


FIG. 1. LEFT VENTRICULAR THERMODILUTION CURVES. The upper part of the figure illustrates general morphology of the curve with rapid fall in aortic blood temperature on injection, followed by stepwise return in temperature. Temperature scale was linear with deflection of  $0.07^{\circ}\text{C}$  per cm. To assure as complete indicator mixing as possible, measurements were not begun until the fourth beat after injection (10). Because the early part of the curve was not analyzed during the mixing beats, this portion of the curve was deliberately allowed to run off scale to obtain full-scale sensitivity for measurement of ratios from the fourth beat on. The ratio of each pair of steps was measured in millimeters above initial base line. The base line for each curve is shown to the left at the point of the arrow signifying indicator injection. Curves obtained in patients AMc and FS are illustrated.

During any given study period, five to ten aortic thermodilution curves (Figure 1) and usually two indocyanine green dilution curves for cardiac output were recorded within as short a time as possible (2 to 3 minutes), along with simultaneous arterial and left ventricular pressure recordings. Ventricular end-diastolic pressure (postatrial contraction) was measured at high gain. Duplicate cardiac outputs recorded at a brachial artery after left ventricular dye injection agreed within 9%. Stroke volumes were determined from heart rate. Two to 6 ml of cold saline was injected into the left ventricle for each thermodilution curve. The relative change in temperature on successive beats ( $t_n/t_{n-1}$ ) was obtained as an average of steps beginning with the fourth beat following indicator injection (to allow indicator mixing) (10). Observations were made at rest

in all subjects, during norepinephrine infusion (8 to 48  $\mu\text{g}$  per minute) in nine (total, 12 observations), and during isoproterenol infusion (0.6 to 2.6  $\mu\text{g}$  per minute) in 16.

End-diastolic volume (EDV) was calculated from the following equation:

$$\text{EDV} = \frac{\text{SV}}{1 - \left(\frac{t_n}{t_{n-1}}\right)},$$

where SV = stroke volume obtained from indocyanine green dilution curves,  $t_n$  = temperature difference from base line of mixed aortic blood on the  $n$ th beat, ESV (end-systolic volume) = EDV - SV, and  $t_n/t_{n-1}$  = ESV/EDV = residual volume fraction.

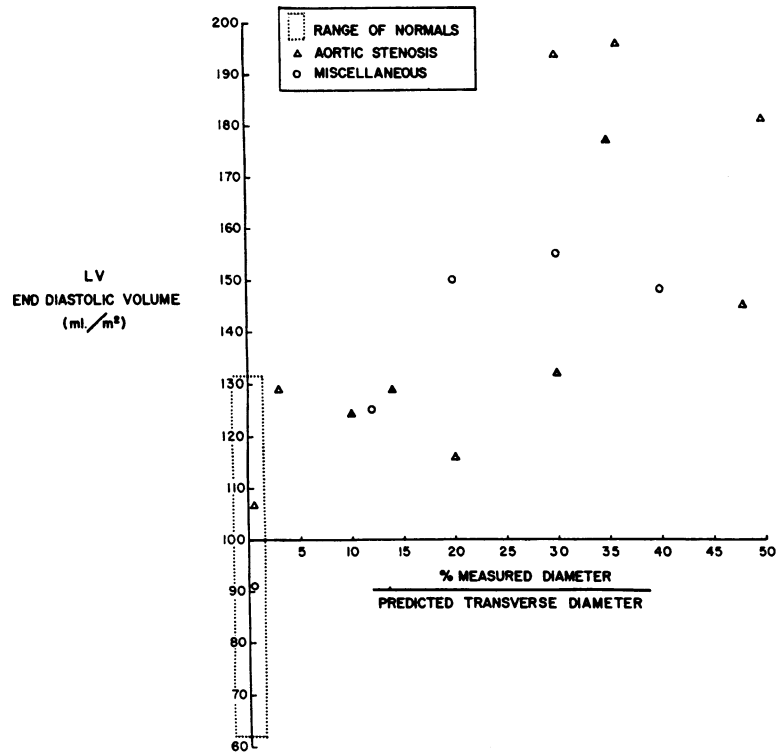


FIG. 2. COMPARISON OF LEFT VENTRICULAR END-DIASTOLIC VOLUME WITH ROENTGENOGRAPHIC ESTIMATION OF HEART SIZE. Cardiac enlargement was judged from the percentage of increase (above 10%) in measured over predicted cardiac transverse diameter (9). The range of the normal group with normal-sized hearts is shown as a rectangle along the ordinate. In general, increase in left ventricular volume followed increase in transverse diameter.

Data used to calculate  $(t_n/t_{n-1})$  had to meet criteria previously set forth, including stepwise decay and reproducibility (7). The ratios reported represent the average of 15 to 30 ratios taken from all satisfactory thermodilution curves in each state.

*Calculations for force and fiber shortening.* It would be useful if the volume to be reported could be fit into a geometric form susceptible to easy force and motion analysis. Burch, Ray, and Cronvich suggested the sphere for this purpose (11). Others have proposed from angiographic study that the left ventricle be represented as an ellipsoid (2, 3, 12). Ventricular wall forces, stresses, and circumferential shortening will vary with curvature in a non-spherical chamber. The problems raised by the choice of the appropriate geometric form, however, can in part be mitigated as follows: 1) The force acting upon the wall of the intact canine left ventricle calculated directly from the intraventricular pressure and inner radius at the transverse equator of the chamber ( $\pi r^2 P$ ) correlated well with wall force directly recorded from a strain gauge (13). These strain gauges were oriented on the ventricular wall in both perpendicular and parallel fashion to the equator, corresponding to minimal and maximal lines of tensile force

(14), without altering the correlation. This suggests that even if the principal forces are not equal, at least they change directionally and linearly together.

2) The over-all changes in force for enlarging shells of both spherical and ellipsoidal shape are similar. The Appendix demonstrates a geometrical analysis of an ellipsoid of revolution (or a prolate spheroid). With a major-minor axis of 2:1 (similar to that of the human heart (14)), total force<sup>3</sup> exerted against the inner surface of such a shell differed by only 8% from that bearing upon a sphere containing an equal volume (Figure A2). The variation in difference in calculated force for varying axis ratios in the physiologic range was less than 10%. Mean systolic tensile force<sup>4</sup> ( $\bar{F}$ ), the average mural force during systole, which theoretically opposes the radial forces bearing upon the endocardial surface of the heart, has been calculated as follows:  $\bar{F} = 4\pi \times \bar{r}^2 \times P_{sm} \times 1,332$  dyne/cm<sup>2</sup>, where  $\bar{r}$  = mean systolic radius of the left ventricle, in

<sup>3</sup> Defined as the product of chamber pressure and inner surface area of shell.

<sup>4</sup> See Appendix regarding error of using average values of pressure and radius.

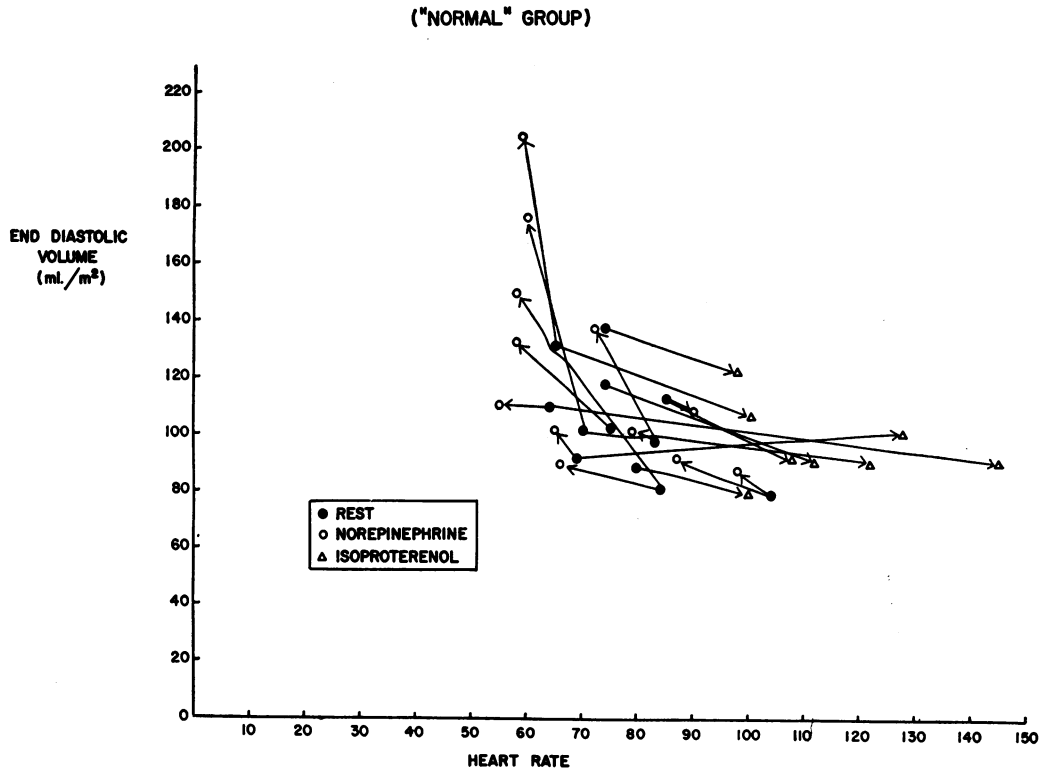


FIG. 3. HEART RATE PLOTTED AGAINST END-DIASTOLIC VOLUME. These tend to vary inversely when resting studies are compared. This is made more evident when norepinephrine or isoproterenol is administered. By the use of binomial distribution the probability that rate and volume will not vary inversely is less than 1 in 1,000 in the "normal" group (16).

centimeters;  $P_{sm}$  = mean systolic pressure of the left ventricle, millimeters Hg; and 1,332 = conversion factor from millimeters Hg to dyne per square centimeter.

Based on published curves of changing left ventricular dimensions and instantaneous aortic blood flow (15), mean systolic radius was estimated as the sum of end-systolic radius ( $es_r$ ) and 0.25 ( $ed_r - es_r$ ), where  $ed_r$  = end-diastolic radius. If ventricular emptying is more uniform throughout the ejection phase, then this method will result in underestimation of the average radius, and consequently, the average volume and force. In addition, mean systolic radius will be a function of the rate of early vs. late systolic ejection. Nevertheless, the error introduced into the calculation of mean force by these considerations is usually small, as shown in the Appendix (Figure A3).

Mean circumferential shortening rate (MCSR) is the average rate of shortening along the inner circumference at any equator of the theoretical sphere and is meant to represent the mean velocity of fiber shortening (not contractile element shortening). Such a representation seems justified because a triplanar shortening pattern has been documented in man (14). MCSR is calculated as follows:  $MCSR = 2\pi(ed_r - es_r)/sep$ , where  $ed_r$  = end-diastolic radius, in centimeters;  $es_r$  = end-systolic radius, in centimeters; and  $sep$  = systolic ejection period, in seconds.

Errors introduced by averaging events of shortening are discussed in the Appendix. The fact that mean and not instantaneous changes in force and fiber velocity are determined by this method decidedly limits the extent of interpretation possible. As shown earlier, however, mean systolic force and shortening rate are less affected by the pattern as opposed to the extent of ventricular emptying.

## Results

*Resting observations.* Comparison between end-diastolic volume and transverse diameter measured by roentgenogram is shown in Figure 2.

*Normal left ventricle (Table I).* End-diastolic and end-systolic volumes in group A averaged 96 (range, 62–131) and 54 (range, 32–78) ml per  $m^2$ , respectively, with an average residual volume fraction of 0.56 ( $\pm 0.057$ ). Findings for the normal category as a whole were similar except for a somewhat larger residual fraction (0.62). Resting heart rate and end-diastolic volume

TABLE I  
Resting values for normal left ventricular volume\*

Patient	Age	BSA	Diagnosis	Volume		ESV EDV	Heart rate	End- diastolic pressure
				End diastolic	End systolic			
		<i>m</i> <sup>2</sup>		<i>ml/m</i> <sup>2</sup>			<i>min</i>	<i>mm Hg</i>
Group A								
1. DG	22	1.98	Normal	131	69	0.53	65	7
2. GS	15	2.00	Normal	109	53	0.49	64	8
3. MaJ	18	1.58	Normal	80	47	0.60	84	6
4. DT	41	2.20	Normal	97	53	0.55	68	10
5. RW	20	1.73	Normal	118	59	0.50	58	11
6. IR	30	1.56	Normal	110	78	0.61	96	4
7. AS	39	1.62	Normal	75	41	0.63	75	8
8. IL	50	1.46	MS, MVA = 2.2 cm <sup>2</sup>	80	46	0.58	76	10
9. LD	27	1.32	MS, MVA = 2.2	108	53	0.49	75	10
10. DH	38	1.46	MS, MVA = 1.7	94	61	0.66	108	5
11. PM	45	1.86	MS, MVA = 1.6	62	32	0.51	72	7
12. AM	49	1.70	MS, MVA = 1.5	87	50	0.58	81	8
Subaverage ± SD				96 20	54 12	0.56 0.057	77 14	8 2
Group B								
13. AMc	49	1.70	MS, MVA = 1.2	87	50	0.58	80	8
14. VB	30	1.75	MS, MVA = 1.0	137	97	0.70	74	16
15. EF	45	1.66	MS, MVA = 0.7	97	72	0.74	83	1
				114	86	0.75	81	1
16. JV	45	1.41	MS, MVA = 0.5	102	76	0.75	75	1
17. ED	46	1.60	ASD, P/S = 3/1	108	81	0.75	85	5
18. LB	44	1.62	AS, AVA = 2.2 cm <sup>2</sup>	78	44	0.57	104	2
19. BD	33	1.60	AS, AVA = 1.0	101	62	0.62	70	14
20. PK	57	1.84	AS, AVA = 1.1	113	87	0.79	65	10
21. FC	20	1.92	AS, AVA = 0.9	91	61	0.67	69	12
22. EM	46	1.55	AS, AVA = 0.8	117	79	0.66	74	9
Total average ± SD				100 18	63 17	0.61 0.095	77 12	8 4

\* MS = mitral stenosis, AS = aortic stenosis, MVA = mitral valve area, AVA = aortic valve area, ASD = atrial septal defect, and P/S = pulmonic/systemic ratio. ESV = end-systolic volume; EDV = end-diastolic volume.

TABLE II  
Resting values for left ventricular volume in aortic stenosis

Patient	Age	BSA	Volume		ESV EDV	Heart rate	End- diastolic pressure
			End diastolic	End systolic			
		<i>m</i> <sup>2</sup>	<i>ml/m</i> <sup>2</sup>			<i>min</i>	<i>mm Hg</i>
1. CS	47	1.52	129	98	0.76	84	9
2. JP	34	2.00	107	79	0.73	116	7
3. AP	55	1.48	124	95	0.76	77	9
4. AS	63	1.79	129	98	0.76	66	21
5. RB	57	1.82	116	82	0.71	99	27
6. EB	38	1.52	132	105	0.80	65	14
7. SC	64	1.66	177	149	0.84	83	10
8. FS	58	1.78	194	161	0.83	71	20
9. MS	51	1.80	181	161	0.89	89	26
10. LM	59	1.55	196	165	0.84	66	40
11. JC	42	1.90	145	123	0.85	74	38
Average ±SD			148 33	120 33	0.80 0.06	81 16	20 12

TABLE III  
*Miscellaneous studies of left ventricular volume*

Patient	Age	BSA	State*	Volume		ESV EDV	Heart rate	End- diastolic pressure
				End diastolic	End systolic			
		<i>m</i> <sup>2</sup>		<i>ml/m</i> <sup>2</sup>			<i>min</i>	<i>mm Hg</i>
Myocardial failure								
1. JA	20	2.20	R	148	136	0.92	88	32
2. MN	43	1.60	R	150	127	0.85	97	18
3. RaB	26	1.57	R	125	108	0.86	85	19
Subaortic stenosis								
1. TT	22	1.50	R	91	49	0.54	77	14
2. JL	42	1.98	R	67	41	0.62	87	6
Paroxysmal tachycardia								
1. ER	61	1.68	R Pat	155 113	136 102	0.88 0.90	90 185	5 6

\* R = rest; Pat = paroxysmal atrial tachycardia.

TABLE IV  
*Effect of norepinephrine on normal left ventricular volume*

Patient	State	Volume		ESV EDV	Heart rate	End- diastolic pressure
		End diastolic	End systolic			
		<i>ml/m</i> <sup>2</sup>			<i>min</i>	<i>mm Hg</i>
1. DG	R	131	69	0.53	65	7
	N	204	106	0.52	59	14
2. GS	R	109	52	0.48	64	8
	N	110	40	0.36	55	12
3. MaJ	R	80	47	0.60	84	6
	N	89	47	0.54	66	12
	N	149	84	0.57	58	14
4. LB	R	78	44	0.57	104	2
	N	87	45	0.52	98	8
	N	91	48	0.52	77	15
5. BD	R	101	62	0.62	70	14
	N	176	139	0.79	60	24
6. ED	R	112	79	0.71	85	5
	N	108	81	0.75	90	8
7. EF	R	97	72	0.74	83	1
	N	101	78	0.77	79	4
	N	137	106	0.78	72	4
8. JV	R	102	76	0.75	75	1
	N	132	98	0.74	58	8
9. FC	R	91	61	0.67	69	12
	N	101	66	0.67	65	14
Average, rest (R)		100	63	0.63	78	6
Average, norepinephrine (N)		124	78	0.63	71	12
± SD, R		17	13	0.14	13	5
± SD, N		37	31	0.14	15	6

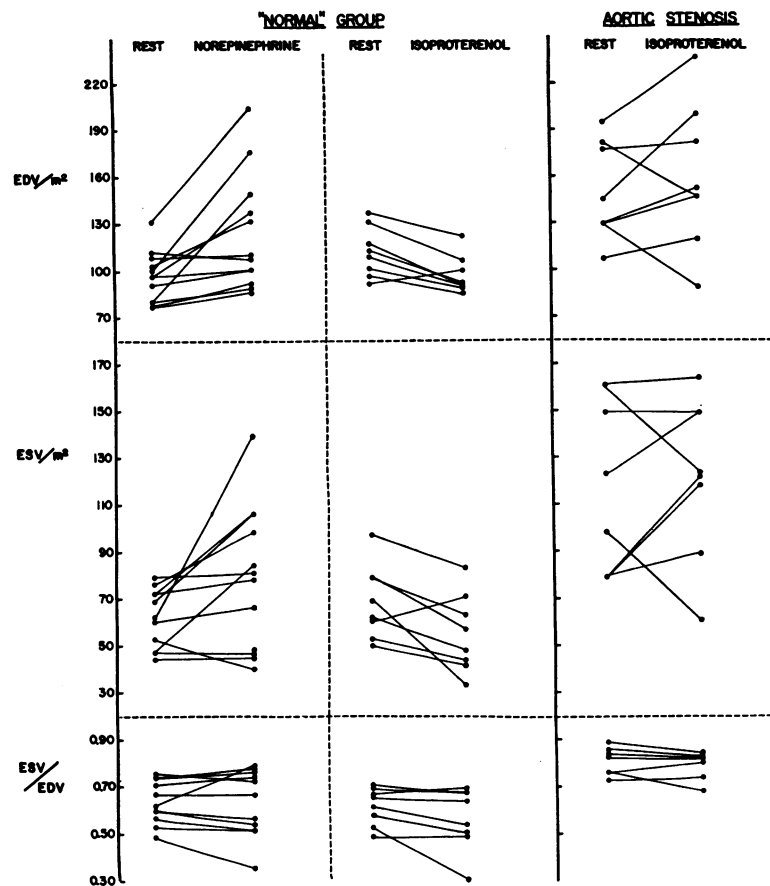


FIG. 4. EFFECT OF NOREPINEPHRINE AND ISOPROTERENOL ON LEFT VENTRICULAR VOLUME. EDV = end-diastolic volume; ESV = end-systolic volume. Norepinephrine increased volumes in the majority of the normal group, and with but two exceptions had little effect on residual fraction. In the normal group, isoproterenol almost uniformly reduced end-diastolic and end-systolic volumes and residual fraction. The response to isoproterenol was different in aortic stenosis: the majority showed increased volume and unchanged residual fraction.

tended to vary inversely, with a borderline significant correlation ( $r = 0.42$ ; SE of the mean  $\pm 0.21$ ;  $p = 0.06$ ).

*Aortic stenosis* (Table II). Although ventricular end-diastolic volume averaged 148 ml per  $m^2$ , or almost 50% greater than the normal group, 6 of the 11 patients had values in the upper portion of the normal range ( $< 132$  ml per  $m^2$ ). On the other hand, residual fraction was almost invariably increased ( $0.80 \pm 0.06$ ).

*Congestive failure* (Table III). Three patients with heart failure of undetermined cause had increases in heart volume with marked increase in residual fraction.

*Subaortic stenosis* (Table III). Two patients had normal heart volumes and residual fractions.

*Paroxysmal atrial tachycardia* (Table III). In one patient (ER) an increase in rate from 90 to 185 resulted in marked fall in both end-diastolic and systolic volumes and virtually no change in residual fraction.

*Effect of norepinephrine on normal left ventricle* (Table IV, Figure 4). End-diastolic and systolic volumes increased over control values in 11 of 12 observations ( $p < 0.01$ ), with an average unchanged residual fraction of 0.63. Progressive increase in volume occurred with increasing doses of norepinephrine in three sub-

TABLE V  
 A. Effect of isoproterenol on normal left ventricular volume. B. Effect of isoproterenol on left ventricular volume in aortic stenosis

Patient	State	Volume		ESV EDV	Heart rate	End- diastolic pressure
		End diastolic	End systolic			
		ml/m <sup>2</sup>			min	mm Hg
A.						
1. DG	R	131	69	.53	65	7
	I	106	33	.31	101	6
2. GS	R	109	53	.49	64	8
	I	90	44	.49	145	0
3. BD	R	101	62	.62	70	14
	I	89	48	.54	122	1
4. ED	R	112	79	.71	84	5
	I	91	63	.68	108	3
5. AMc	R	87	50	.58	80	8
	I	83	42	.51	104	7
6. VB	R	137	97	.70	74	17
	I	122	83	.68	98	8
7. FC	R	91	61	.67	69	12
	I	100	71	.70	128	10
8. EM	R	117	79	.66	74	9
	I	90	57	.64	112	11
Average, rest (R)		111	69	.62	72	10
Average, isoproterenol (I)		96	55	.56	115	6
± SD, R		16	13	.09	7	4
± SD, I		13	15	.13	16	5
B.						
1. CS	R	129	98	.76	84	9
	I	89	61	.68	119	8
2. JP	R	107	79	.73	116	7
	I	119	89	.74	125	8
3. AS	R	129	98	.76	66	21
	I	151	122	.81	95	30
	I	146	118	.81	103	30
4. SC	R	177	149	.84	83	10
	I	181	149	.82	100	11
5. FS	R	194	161	.83	71	20
	I	237	164	.83	160	22
6. JC	R	145	123	.85	74	38
	I	199	164	.83	96	—
7. MS	R	181	161	.89	89	26
	I	146	123	.84	100	14
Average, R		152	124	.81	83	22
Average, I		160	124	.80	112	27
± SD, R		33	34	.06	17	12
± SD, I		46	36	.06	22	16

jects. Heart rate decreased as volume increased (Figure 3).

*Effect of isoproterenol on normal left ventricle and left ventricle in aortic stenosis (Table VA and B; Figure 4).* End-diastolic and systolic volumes decreased in seven of eight normal studies ( $p < 0.05$ ), with reduction in residual fraction in most instances ( $0.05 < p < 0.1$ ). Heart rate increased in all subjects as volume decreased (Figure 3).

In contrast to the normal group, end-diastolic volume in aortic stenosis subjects increased in

six of eight measurements (Figure 4). Although the increase for the group was not statistically significant, the average difference in response between the aortic stenosis and normal subjects was significant ( $p = .005$ ). The end-systolic volume changed directionally with end-diastolic volume. Residual fraction was essentially unchanged in all but patients CS and MS.

*Relationship between end-diastolic pressure and volume.* Directional changes were similar in the majority of normal subjects (Figure 5A). The few discrepancies usually occurred when very



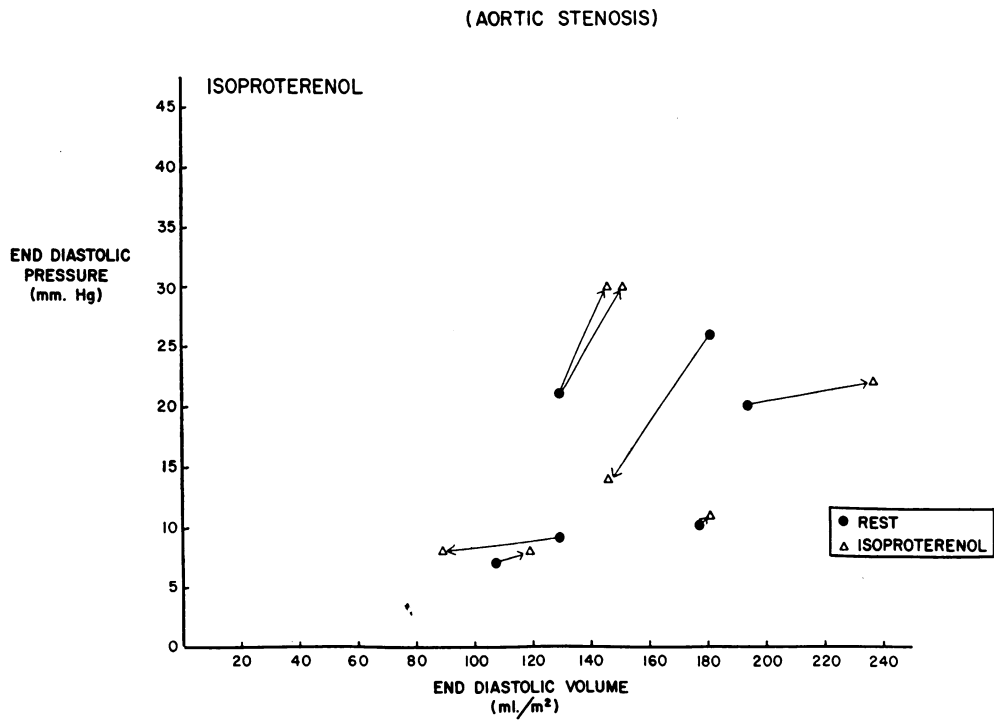
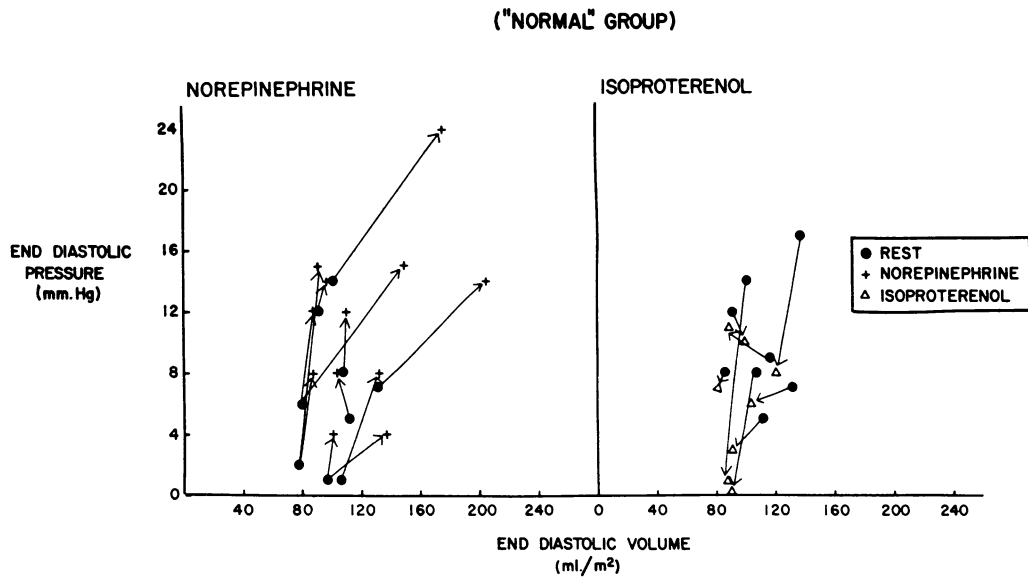


FIG. 5. CHANGE IN END-DIASTOLIC PRESSURE AND VOLUME DURING NOREPINEPHRINE AND ISOPROTERENOL INFUSION.

NORMAL GROUP. Resting values show only a scatter. Major changes in end-diastolic pressure often occurred with only minor changes in end-diastolic volume.

AORTIC STENOSIS GROUP. Consonant directional changes occurred in volume and pressure, but much greater individual variation occurred in the magnitude of each change, suggesting differences in compliance.

TABLE VI  
Average values for left ventricular dimensions and force

State	End-dias- tolic circumference	Circum- ferential shortening distance	Percent- age of shortening	Circum- ferential shortening rate	Mean systolic force
	cm	cm	%	cm/sec	dyne/beat ( $\times 10^6$ )
Normal LV*					
Patients 1-7†	R‡	22.3	4.0	18	17
Total group	R	21.5	3.2	15	18
	N	22.8	3.4	15	28
	R	22.6	3.2	14	22
	I	21.5	3.7	17	20
Aortic stenosis	R	25.0	1.7	8	36
	I	25.3	1.9	8	43
Myocardial failure	R	24.5	1.0	4	26

\* Left ventricle.

† These patients, who had no detectable disease, have been averaged separately to define normal values.

‡ R = rest, N = norepinephrine, and I = isoproterenol.

small differences were measured between pairs of pressures and volumes.

Two aortic stenosis subjects had elevated end-diastolic pressures with normal end-diastolic vol-

umes (Table II), suggesting a difference in ventricular compliance from the normal group.

Patient SC, on the other hand, had normal end-diastolic pressure associated with a greatly in-

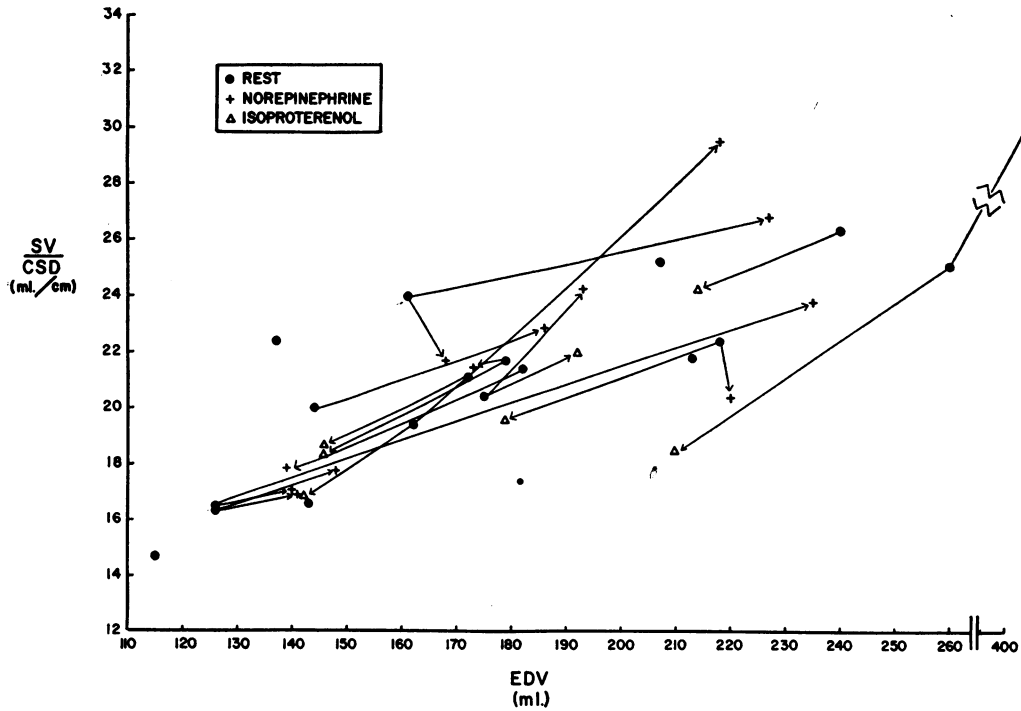


FIG. 6. STROKE VOLUME (SV) PER UNIT CIRCUMFERENTIAL SHORTENING DISTANCE (CSD) PLOTTED AGAINST END-DIASTOLIC VOLUME (EDV). Although the variables are interdependent, this graph illustrates quantitatively the geometric principle that a greater volume (V) is ejected per unit decrease in circumference ( $2\pi r$ ) the larger the shell at the onset of contraction ( $dV = 4\pi r^2 dr$ ).

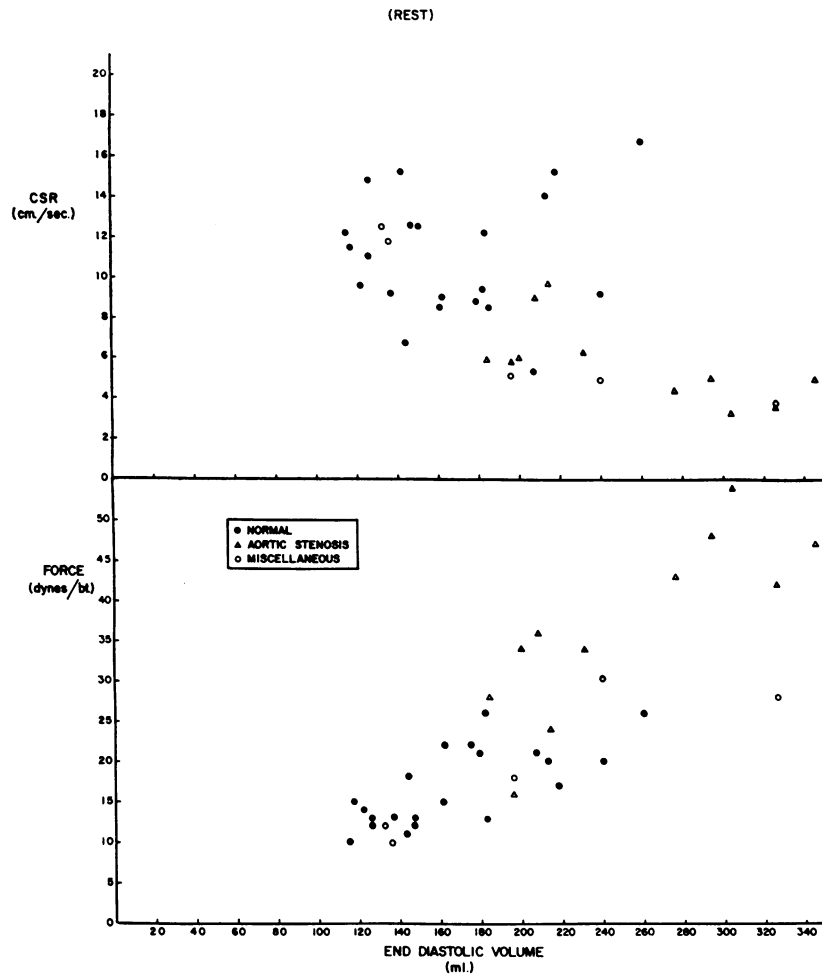


FIG. 7. DIFFERENCE IN DEGREE OF DEPENDENCE UPON END-DIASTOLIC VOLUME OF MEAN SYSTOLIC FORCE AND CIRCUMFERENTIAL SHORTENING RATE (CSR). Force (dyne  $\times 10^6$ ), primarily a function of volume and pressure, showed a high correlation ( $0.87 \pm 0.17$ ). Shortening rate (centimeters per second), which depends on both time and distance of shortening, showed a lesser correlation ( $0.52 \pm 0.17$ ) ( $p < 0.005$ ) (16).

creased end-diastolic volume. With isoproterenol, consonant changes occurred in all subjects (Figure 5B).

*Circumferential shortening during systole.* In those subjects virtually free of heart disease (Patients 1 to 7), the left ventricle shortened an average of 18% of initial or end-diastolic circumference (Table VI). The percentage was decreased in aortic stenosis and heart failure. The greatest percentage of shortening occurred in GS during norepinephrine infusion (29%).

*Effect of heart size on stroke volume ejected per unit shortening distance.* Figure 6 shows

that the ratio of stroke volume to shortening distance decreased when heart size decreased during isoproterenol infusion and increased with increase in heart size during norepinephrine infusion.

*Mean systolic force and mean circumferential shortening rate.* Table VI and Figure 7 show, as expected, that mean systolic force increased with increasing degree of heart disease and directly with cardiac size. Shortening rate showed an inverse relationship (Table VI), but with more scatter (Figure 7), and a significantly lower degree of correlation with end-diastolic volume than force with end-diastolic volume ( $p < .005$ )

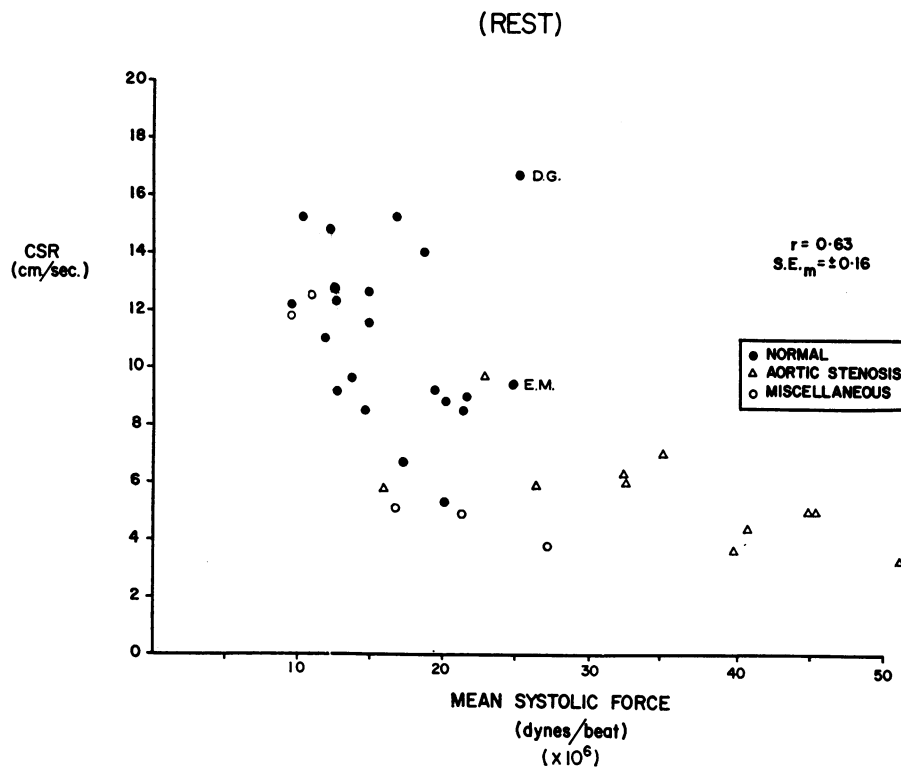


FIG. 8. MEAN SYSTOLIC FORCE PLOTTED AGAINST CIRCUMFERENTIAL SHORTENING RATE. The inverse correlation is primarily a function of the mutual dependence on volume of the two plotted values. The graph serves, however, to indicate how critical cardiac size becomes to total force development. Note the constant shortening rate in aortic stenosis despite varying degrees of total force ( $\text{dyne} \times 10^6$ ).

(16). Figure 8 indicates the inverse relationship between force and shortening rate ( $r = 0.63 \pm 0.16$ ). Note the scatter, however, and in particular, the unchanged circumferential shortening rate while force increased in the points dominated by the aortic stenosis subjects.

*Effect of catecholamines (Figure 9).* Norepinephrine increased systolic force in all experiments, but circumferential shortening rate rose in only three of nine. With isoproterenol, when force changed little, shortening rate invariably increased, the highest value being 41 cm per second in DG (or more than twice the control). Isoproterenol, however, caused little increase in shortening either in subjects with large end-diastolic volumes (FS, MS) or in those in whom force increased excessively (AS, JC) (similar to norepinephrine response). The highest calculated mean forces were obtained in these latter subjects.

## Discussion

*Resting left ventricular volume.* There are relatively few figures in the literature with which to compare the values found in our 12 subjects considered to have nearly normal left ventricles. Folse and Braunwald (17), using an isotope dilution technic, found a normal volume of 89 ml per  $\text{m}^2$ . Arvidsson (2) described much smaller volumes using an angiocardiographic method in a variety of pathological conditions. He found end-diastolic volumes to range from 39 to 94 ml per  $\text{m}^2$  irrespective of the presence of such diseases as hypertension or aortic stenosis.

The normal residual fraction varied widely, but it is probably significant that the left ventricle emptied nearly half its volume in those subjects with no recognizable heart disease (Table I, group A). Again, the residual fractions reported herein differ from those of Arvidsson, who found

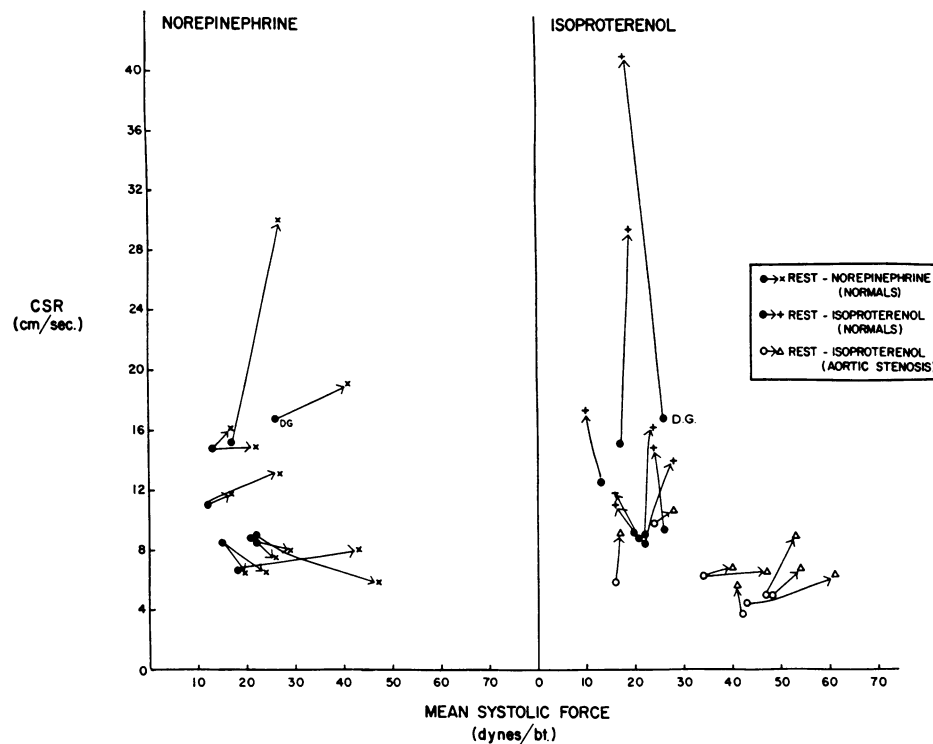


FIG. 9. EFFECT OF NOREPINEPHRINE AND ISOPROTERENOL ON MEAN SYSTOLIC FORCE AND CIRCUMFERENTIAL SHORTENING RATE. With norepinephrine only two subjects showed substantial increase in shortening rate (CSR) as force (dyne  $\times 10^6$ ) increased. This is in sharp contrast to the general increase in shortening rate seen when mean force was unchanged during isoproterenol stimulation. Force did increase, however, in five of the seven aortic stenosis subjects given isoproterenol. Shortening rate did not materially increase in four of the five.

a residual fraction of only 0.25 (range, 0.05–0.44), even in the presence of disease. In fact, this investigator suggested that the angiocardigraphic method was probably more accurate for measuring end-diastolic rather than end-systolic volume, although he did show a good correlation between direct Fick and angiocardigraphic outputs. On theoretical grounds, however, a resting residual fraction of 0.25 seems too low. This would presuppose an average percentage of shortening of over 35% of initial circumference.<sup>5</sup> Sonnenblick, Spiro, and Cottrell (18) have shown that cat papillary muscle, when taken through its complete range of action (from peak to zero tension development), has a total change in length only 32% of the length at peak tension. This percentage of shortening (29%) was approached

<sup>5</sup> This represents only the minimal degree of shortening required of the average sarcomere, as the sarcomeres are obviously not all oriented in vectors parallel to the circumference.

in GS during catechol stimulation, and it would seem unlikely that the entire range of shortening would be utilized in the resting state alone. The results of the dilution method used herein have been verified directly by post-mortem measurements in the dog (7). Furthermore, a realistic directional change has been shown between observed X-ray cardiac size and calculated volume (Figure 2). These differences in results are unreconciled at present.

The reduced stroke volume characteristic of tight mitral stenosis (19) has been attributed to reduced ventricular filling during diastole and consequent diminution in emptying during systole. The finding of normal instead of reduced end-diastolic volume in the subjects with mitral stenosis tends to vitiate this explanation.

As shown in the normal left ventricle group, mild aortic stenosis has no effect on ventricular volume. Severe aortic stenosis, on the other hand, can exist with either a normal or an in-

creased resting diastolic volume. This is corroborated by X-ray study of the degree of cardiac enlargement (Figure 2), which agreed closely with the end-diastolic volume measurement. In contrast to the normal left ventricle subjects, in general, and to those with mild aortic stenosis, in particular, residual fraction was uniformly increased regardless of left ventricular diastolic volume. All but two patients had clinical symptoms consistent with left ventricular failure, and left ventricular end-diastolic pressure was usually elevated. These data emphasize that pulmonary congestive symptoms may exist in aortic stenosis despite a completely normal left ventricular volume. Whether or not this is true heart failure is unknown.

Similar findings regarding diastolic volume and residual fraction were made in three subjects with heart failure of unknown cause, as previously reported (17). Increase in residual fraction may be an important functional expression of cardiac failure and, if not related to extremes of heart rate, may be much more significant than an actual increase in ventricular volume. The volume technics provide a new tool for studying not only absolute chamber volume, but also the degree of systolic emptying in various forms of heart disease under diverse conditions. In the two patients with subaortic stenosis, end-diastolic volumes were among the lowest recorded, and fractional emptying was comparable to the normal. The small volume may reflect either an early stage in the disease (i.e., normality), or the extraordinary effects of concentric hypertrophy. The dynamic character of this disorder may be such that accelerated ventricular emptying during the early phase of ejection (before obstruction to outflow becomes severe) permits a normal fraction of end-diastolic volume to be ejected.

The single study of paroxysmal tachycardia illustrates the reduction in ventricular end-diastolic volume with cardiac rate described by Bristow, Mintz, Ferguson, and Rapaport (20) in dogs. A similar trend was seen in the over-all data (Figure 3).

*Influence of catecholamines.* The increase in end-diastolic volume seen in man during norepinephrine infusion was not observed in the anesthetized dog, however (21). The results in man

probably represent the effects of two induced hemodynamic changes: 1) increase in afterload to contraction<sup>6</sup> through rise in arterial pressure and 2) decrease in cardiac rate. Both an increase (22) and no change (23) in ventricular end-diastolic pressure (and presumably volume) have been reported when the isolated left ventricle is confronted with increased resistance to ejection. Bristow and associates (20) reported that ventricular end-diastolic volume increased as heart rate was slowed, but that residual fraction decreased. The essentially unchanged residual fraction in these studies, despite rate reduction and the known cardiac inotropic effects of norepinephrine, implicates the role of increased resistance to ejection in producing much of the observed response. This is further attested to by noting the different effects of isoproterenol in normal as opposed to aortic stenosis subjects.

In normal subjects the decrease in left ventricular volume with a greater fractional emptying during isoproterenol infusion was probably related to 1) decrease in afterload through primary systemic vasodilatation, 2) increase in cardiac rate, and 3) direct inotropic stimulation of the heart. Similar effects were induced with isoproterenol by Bristow, Ferguson, Mintz, and Rapaport (24) and differ from the response to increased heart rate alone (20) by the increased fractional emptying. The response was different, however, in the aortic stenosis group. Mean ventricular volume rose slightly and emptying was unchanged. Whereas left ventricular end-diastolic pressure fell in the normals, it rose or was unchanged in most of the aortic stenosis subjects. This difference in response probably reflected the interaction between the magnitude of fixed resistance to ejection in severe aortic stenosis and the ability of the myocardium to respond to simultaneous inotropic stimulation. Because of the increased afterload, the ventricular response was more like the normal response to norepinephrine, whereas peripheral vasodilatation and hypotension led to concurrent reflex tachycardia.

*Relationship of ventricular end-diastolic vol-*

<sup>6</sup> Afterload is defined as ventricular wall tension during systole generated by the interaction of ventricular contraction and outflow resistance.

*ume and pressure.* There were frequent isolated abnormalities either in pressure or volume in the aortic stenosis group, undoubtedly reflecting major differences in compliance between patients. For example, patient RB had a markedly elevated left ventricular end-diastolic pressure and normal end-diastolic volume, whereas SC had just the opposite findings. Similar observations in idiopathic myocardial hypertrophy (25) and in valvular heart disease (26) have been made. Variations in compliance among normal subjects probably do occur also as illustrated in Figure 5. Correlations of this type are limited, however, both by errors of the volume method and by errors in recording end-diastolic pressures. This latter value is subject not only to the vagaries of recording through a catheter but to artifacts inapparent to the investigator, introduced by changes in respiration. Attendant effects on the intrathoracic pressure to which the heart is exposed can alter the base line and therefore the apparent left ventricular end-diastolic pressure.

End-diastolic tension, the preload to ventricular contraction, is of great theoretical importance. The aforementioned source of errors, however, vitiates interpretation of all but large changes in this derived value. Such calculations were not made in this study.

*Ventricular systolic force and fiber shortening.* Ventricular systolic pressure and ejection volume are secondary derivatives of mechanical events that occur within the wall of the heart. These are, respectively, the total force developed and the distance through which the fiber shortens; in turn, these reflect the interaction between the contractile element and the elastic structures comprising muscle fiber (27). If ventricular size and shape are known, then both force and linear shortening of the heart can be assessed during contraction. The method employed herein supplies volume only. As described in the Appendix, however, so long as total force and not stress is the issue, a spherical shell can be used to contain the volume.

Increase in ventricular size obviously increases systolic force per unit pressure developed and decreases the systolic shortening per unit ejection volume. Thus, although force and shortening rate are derived in part from independent varia-

bles, diastolic volume is common to both. There must be then a trend toward an inverse relationship between the two when multiple points are compared (Figures 7 and 8). Individuals will vary, however. For example, DG exhibited a much faster shortening rate than did EM for the same force. Also, in the aortic stenosis subjects, shortening rate tended to be relatively constant despite ever increasing values of force.

The different effects of catechols on the heart can be described by the force-circumferential shortening rate relationship. Despite its known inotropic actions, when norepinephrine was given systemically, only in the minority of experiments was an increase in velocity of fiber contraction seen. Presumably, the increased afterload to contraction obscured the usual evidences of inotropic action. Although the force-velocity relationship of the contractile element may have changed to keep mean fiber velocity constant as force increased, the net result to the heart was unchanged fiber contraction. In contrast, isoproterenol (which did not materially affect mean force in the normals) caused marked increase in circumferential shortening rate. Considering the usual reduction in heart size (and therefore decrease in initial length) seen with isoproterenol, the increased fiber shortening rate must have come from an inotropic stimulus<sup>7</sup> to the contractile element. Inhibition of this effect, if force is greatly increased, was seen in those aortic stenosis subjects in whom isoproterenol resulted in increased force or afterload.

### Summary

- 1) Left ventricular volume has been studied in 39 human subjects by the thermodilution technic. Observations were made at rest and during infusion of norepinephrine and isoproterenol.
- 2) The average end-diastolic volume in 12 subjects with the least cardiac disease was  $96 \pm 20$  ml per m<sup>2</sup> with an end-systolic (residual) fraction of 0.56.
- 3) End-diastolic volume was normal in mitral stenosis.
- 4) Severe aortic stenosis was associated with either normal or increased end-diastolic volume. Residual fraction, however, was

<sup>7</sup> Although this probably represented direct catechol effect on contractile element, increased inotropism from increased heart rate per se cannot be ruled out (28).

invariably increased in this disease and in subjects with heart failure due to other causes. 5) Norepinephrine infusion increased end-diastolic volume in the normal group. Isoproterenol decreased end-diastolic volume in the normal group, but tended to increase volume in subjects with aortic stenosis. This difference in response was attributed to the fixed resistance of aortic stenosis acting to cause intraventricular hypertension, which was not seen in other subjects. 6) Mathematical evidence has been presented to indicate under what circumstances the spherical model may validly be used for structural analysis of volume changes. Mean systolic force and mean shortening rate of the left ventricle can be determined, but ventricular stresses cannot be accurately assessed. 7) Force-shortening rate analysis has shown that shortening rate increased in all normal subjects given isoproterenol, but was virtually unchanged in six of nine subjects given norepinephrine and in six of seven subjects with severe aortic stenosis given isoproterenol. The significance of these findings is discussed.

### Appendix

*Calculation of mean force, mean fiber shortening, and stress of the left ventricle.* The purpose of this Appendix is to determine to what extent both shape of the left ventricle and time-averaging of contractile events distort conclusions derived by use of a spherical ventricular model.

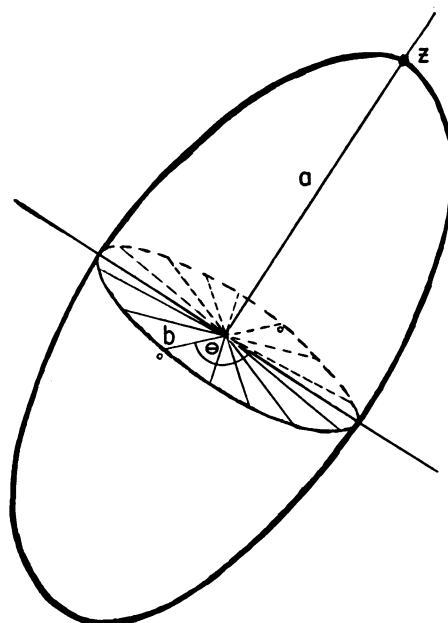
*Mean force.* The final vector of ventricular contraction is the delivery of a force that acts at the endocardial surface to impart pressure to the blood in the cavity. The pressure generated depends on the magnitude of this final force and the total surface area so affected, and it is not affected by the wall thickness or muscle mass which produces the force. Empirical studies by Dodge, Sandler, Ballew, and Lord (3) have shown that the left ventricle is essentially a prolate spheroid<sup>8</sup> having a major:minor axis ratio of about 2:1. The surface area of such a shell (Figure A1) may be calculated from the following equation:

$$\text{Surface area} = 2\pi \left( b^2 + ab \frac{\sin^{-1}e}{e} \right),$$

where  $a$  = length of major semiaxis of ellipse;  $b$  = length of minor semiaxis; and  $e$  = eccentricity of ellipse,  $e = (a^2 - b^2)^{1/2}/a$ , and  $0 < e < 1$ .

When the axis ratio is 1,  $a$  is equal to  $b$  and  $\sin^{-1}e/e$  is an indeterminate form which can be shown to equal 1,

<sup>8</sup> A prolate spheroid is a shell formed by revolving an ellipse around its long axis.



PROLATE SPHEROID

FIG. A1. PROLATE SPHEROID OF REVOLUTION ABOUT Z-AXIS.  $a$  = length of major semiaxis;  $b$  = length of minor semiaxis;  $\Theta$  = angle between any meridian and reference meridian.

so that the equation so derived  $= 4\pi r^2$  or that of a sphere. When ventricular shape is not known but volume is (as in the dilution method), it has been convenient to use the sphere as the containing shell structure. Figure A2 shows a comparison of total force bearing upon equivolumic prolate spheroids and spheres. On the abscissa are the semiaxis ratios represented by  $= a/b$ . On the ordinate are the force ratios for a given pressure. Note that in the canine and human left ventricular axis range (2:1), the difference between the two forces is only 8%. The spherical model underestimates by this small amount the force within the spheroid. Even more significant is the fact that if the axis ratio of the spheroid itself changes from 2:1 to 3:1, less than 10% additional increase in actual force over the calculated force will occur. Values derived from Hawthorne's data (29),<sup>9</sup> corrected for ventricular wall thickness, indicate a change during contraction of 2.2 to 2.75 in axis ratios. Use of a sphere then realistically introduces little error into calculation of total force even with changes in axis ratio.

Because instantaneous contractile events are virtually immeasurable in man at present except by angiographic technics, neither a force-time curve nor a truly integrated mean force can be calculated. Mean force may be estimated from mean systolic radius and pressure, however. Radius shortening during systole is a small fraction of end-diastolic radius length. For an average sized left

<sup>9</sup> Experiment reported on p. 114.



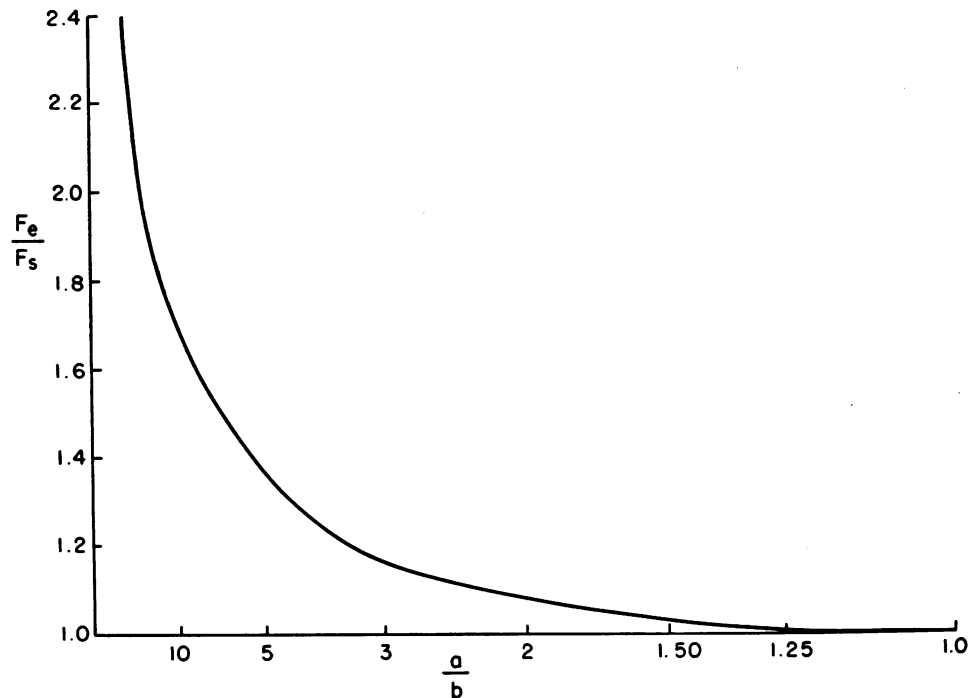


FIG. A2. RATIO OF FORCES OF EQUIVOLUMIC ELLIPSOIDS AND SPHERES ( $F_e/F_s$ ) PLOTTED AGAINST MAJOR:MINOR AXIS RATIO ( $a/b$ ). Note that the flat portion of the curve encompasses physiologic values described for the human and canine heart, i.e., axis ratios between 2:1 and 3:1.

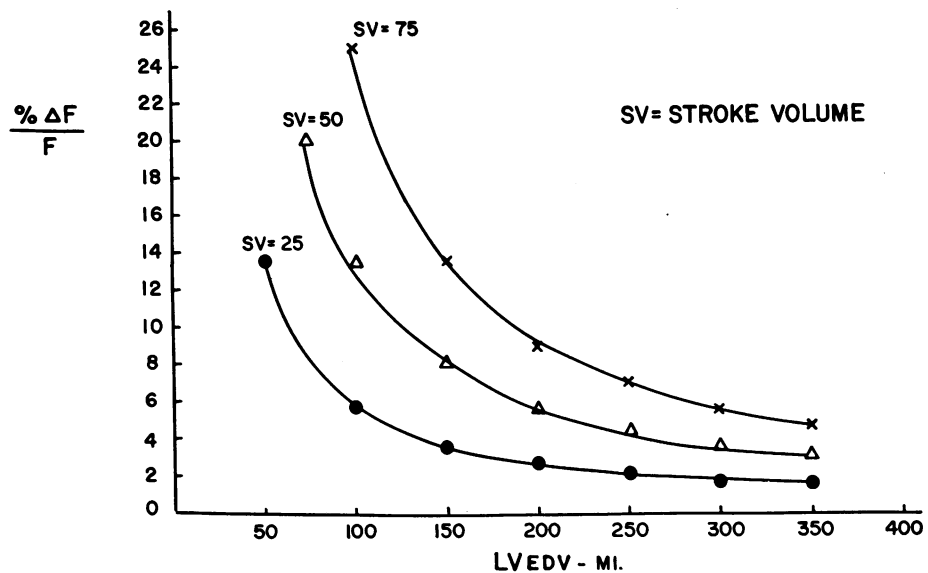


FIG. A3. RELATION OF ERROR IN ESTIMATED MEAN RADIUS TO ERROR IN MEAN FORCE. The abscissa is end-diastolic volume (EDV), and the ordinate is percentage of error in force. Each curve represents degree of error in force possible for a given end-diastolic volume (and degree of emptying) resulting from  $\pm 30\%$  error in estimation of change in radius during systole.

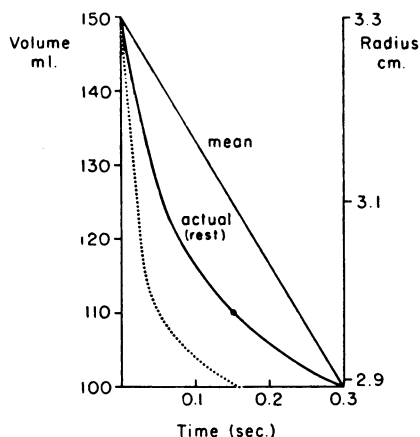


FIG. A4. TIME COURSE OF VENTRICULAR EMPTYING. The abscissa is time in seconds. The left ordinate is ventricular volume (milliliters); the right, ventricular radius (centimeters). The middle (curved) line is the pattern of ventricular emptying (after Rushmer (15)). The straight line is mean rate of emptying as calculated. The lowest (curved) line represents augmented ventricular emptying. Note that the linear (calculated) pattern represents events which, in fact, follow the middle or lower curve. When emptying is complete very early in systole, as shown by the lowest curve, systole is almost invariably shortened.

ventricle emptying 25 to 50% of its volume, the corresponding change in radius length is 8 to 13% of resting length. When ventricular emptying is less than average, radius change is even smaller. Since the range of variation is narrow, a relatively large error in estimating the radius changes during systole will have little effect on the derived mean radius and mean force (Figure A3).

*Mean fiber shortening.* The extent of fiber shortening will vary to some degree at different layers of the ventricular wall. Because thin wall theory is generally applicable to the heart as a shell (14), and because only the final endocardial vector of force is being measured, it is considered acceptable to measure shortening as if it occurred only at the endocardial surface. The time course of ejection, and therefore of shortening, is difficult to determine accurately. On the other hand, the total extent of shortening at any equator of the sphere can be calculated and the mean rate of shortening determined from the duration of systole. To assess errors due to change in time pattern of ejection, Figure A4 was drawn. The middle line represents the curve of decrease in ventricular volume under resting conditions according to Rushmer (15). The straight line to the right indicates the mean rate of shortening (or emptying) as calculated herein. The values derived from this linear rate of volume-decrease represent events which, in fact, occur as a curvilinear function (70 to 80% emptying at  $t_1$ ). If volume ( $V$ ) is considered as a

function of time, then the mean value of  $V(t)$  in the time interval ( $t_{ed}$ ,  $t_{es}$ ) is given by

$$\frac{\int_{t_{es}}^{t_{ed}} V(t) dt}{t_{ed} - t_{es}}$$

If  $V$  could be defined precisely as a function of time, then mean volume during systole could be determined and from this a mean radius that would reflect the variations in ventricular emptying rate. Since only the total change in volume is known, we must use the relation

$$\frac{\Delta V}{\Delta t} = 4\pi r^2 \frac{\Delta r}{\Delta t}$$

where  $\Delta$  is the net change over the entire ejection period. Instantaneous rates of change are not reflected in the mean rate computed over the entire ejection period. Obviously, instantaneous changes are progressively less important if disease or an intervention slows or linearizes the usual pattern of ejection. Conversely, any intervention that increases early ejection will be associated with early termination of systole (30). The shortening of the time interval will affect mean computed rate in a direction similar to change in instantaneous rate. Interpretation of findings becomes meaningful if these facts are borne in mind.

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