

# The Effects of Posture and Isoproterenol on the Velocity of Left Ventricular Contraction in Man

## THE RECIPROCAL RELATIONSHIP BETWEEN LEFT VENTRICULAR VOLUME AND MYOCARDIAL WALL FORCE DURING EJECTION ON MEAN RATE OF CIRCUMFERENTIAL SHORTENING

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**ABSTRACT** A study was performed in five normal men in whom left ventricular volume was measured by thermodilution in the supine and 60° head-up postures, in the control state, and then during steady-state response to isoproterenol. The mean rate of circumferential shortening of the left ventricle was calculated for each of the postures in both inotropic states and was found to remain constant in the control state at  $12.5 \pm 0.6$  cm/sec in the supine posture and  $13.3 \pm 0.5$  cm/sec in the tilted posture. Similarly, mean rate of circumferential shortening remained constant in response to the positive inotropic effect of isoproterenol at  $20.9 \pm 0.5$  cm/sec in the supine position and  $20.7 \pm 0.5$  cm/sec in the tilted posture. It is concluded that the constancy of mean rate of circumferential shortening over the relatively broad physiologic range of left ventricular end-diastolic volume and mean force of ejection during a given state of myocardial contractility represents the coupled reciprocal influences of ventricular wall tension and myocardial fiber length on the velocity of ventricular wall shortening. Unlike stroke work, stroke power, and mean rate of left ventricular ejection, which are volume-dependent parameters of myocardial performance, the mean rate of cir-

cumferential shortening appears to be a reasonable index of left ventricular contractility, which in steady-state conditions is independent of left ventricular end-diastolic volume and mean ventricular wall force of ejection. In this study, changes in mean rate of circumferential shortening associated with changes of heart rate were small and variable.

### INTRODUCTION

Studies of the mechanics of contraction of isolated papillary muscle (1-5) have shown that the relationships between force development, velocity of muscle shortening, and muscle length apply to cardiac muscle in much the same way as has been defined in isolated skeletal muscle (6, 7), and that cardiac muscle has the additional capability of altering its force-velocity relationships (1). In the most recent investigations, techniques of utilizing these observations in the analysis of left ventricular performance in the intact animal heart have been developed (8-12). However, these methods require control of ventricular filling pressure and end-diastolic volume, arterial blood pressure, and heart rate. In the study of left ventricular function in man, it is impractical to control many of the determinants of ventricular performance. Consequently, various indirect approaches to the measurement of left ventricular contractility have been devised. Most prominent among these has been the measurement of the rate of pressure development during the isovolumic contraction period ( $dp/dt$ ). Gleason and Braunwald (13) have used the peak value of this measurement without correction. Frank and Levinson (14) have corrected

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peak  $dp/dt$  for fiber length of the left ventricular wall determined by measurement of left ventricular end-diastolic volume using thermodilution. Mason and coworkers, (15, 16) have extrapolated the calculated values of contractile element velocity from measurements of  $dp/dt$  at a series of points during the pressure-velocity descending limb of isovolumic tension development to zero load, the theoretical value for maximum velocity of shortening of the contractile element ( $V_{max}$ ). Siegel and Sonnenblick (17) have corrected peak  $dp/dt$  by dividing the latter value by the integrated isometric tension, IIT,<sup>1</sup> to provide an index independent of fiber length. It is also possible in such studies to construct indices of ventricular wall force and of velocity of ventricular wall shortening during systole utilizing measurements of left ventricular volume and pressure (18–21). The present investigation was undertaken to determine whether or not it is feasible, utilizing thermodilution to measure left ventricular end-diastolic (LVEDV) and end-systolic (LVESV) volumes (22–25), to apply the concepts of force-velocity and length-velocity relations of isolated cardiac muscle to the assessment of left ventricular adaptation in conscious normal human subjects. In this study, mean left ventricular wall force (MFE) and mean rate of circumferential shortening (MRCS) during ejection were calculated, assuming that the ventricle behaves as a contracting, thin-walled sphere. To evaluate the effects of variations of ventricular wall force and initial length (end-diastolic volume) on velocity of ventricular wall shortening, observations were made in subjects in the supine position in which heart size and MFE are relatively large, and in the 60° head-up tilted posture in which LVEDV and, consequently, MFE are reduced. Observations were then repeated during steady-state response to isoproterenol (I) infusion to assess the additional influence of a positive inotropic intervention.

## METHODS

Five male volunteers<sup>2</sup> without evidence of heart disease, ranging in age from 24 to 40 yr, were given 100 mg pentobarbital orally 2 hr after a light breakfast and were pre-

<sup>1</sup> *Abbreviations used in this paper:* AEDP, end-diastolic aortic pressure; AESP, end-systolic aortic pressure;  $\Delta C$ , circumferential charge during ejection; I, isoproterenol; IIT, integrated isometric tension; LVEDC, left ventricular end-diastolic circumference; LVEDV, left ventricular end-diastolic volume; LVESC, left ventricular end-systolic circumference; LVESV, left ventricular end-systolic volume; LVET, left ventricular ejection time; MAP, mean aortic pressure; MFE, mean left ventricular wall force; MRCS, mean rate of circumferential shortening; MRLVE, mean rate of left ventricular ejection; peak ASP, peak aortic pressure; SP, stroke power; SW, stroke work.

<sup>2</sup> Subjects utilized in this study were from the inmate population of San Quentin Penitentiary (Department of Corrections, State of California). Informed consent was obtained in the form of a signed statement from each subject.

pared for study in the following manner. A small polyethylene catheter (PE 50) was introduced through a No. 17 Courmand needle into the right basilic vein and was advanced until its tip rested in the right atrium. A polyethylene catheter (PE 160), 15 cm in length was introduced percutaneously into the left brachial artery. From this catheter arterial pressure was obtained, and blood was withdrawn through a Gilford densitometer for recording indicator dilution curves after the injection of indocyanine green through the right atrial catheter. Cardiac output was determined by the Stewart-Hamilton method (26, 27). Another polyethylene catheter (PE 160) with a specially preformed tip was introduced percutaneously into the right femoral artery and was advanced until the tip traversed the aortic valve entering the left ventricle. A few ectopic beats generally occurred as the catheter entered the ventricle, but were uncommon during the remainder of the study. Through this catheter, left ventricular pressure was recorded, and cooled normal saline was injected to obtain thermodilution. A thin catheter with a thermistor bead mounted at its tip<sup>3</sup> was introduced through a short polyethylene "sleeve" (PE 160) which had been inserted into the left femoral artery percutaneously. The "sleeve" prevented bleeding which would otherwise have occurred around the thermistor catheter. The "sleeve" was repeatedly flushed and filled with heparinized saline to prevent clotting. A special fitting (B-D 615A) made this possible. The thermistor bead was positioned approximately 2 cm above the aortic valve and was connected as one arm of a Wheatstone bridge and was balanced through a carrier amplifier. Thermodilution curves were recorded after injection of 5–7 ml of cold saline into the left ventricle over a period of several heart beats. This method of injection was chosen because with it there is increased statistical probability of thorough left ventricular mixing before "washout" utilized in calculations. 5–10 such curves, free of ectopic beats, were obtained in each condition of the study. Special precautions were taken to eliminate the risk of embolism: (a) a single hole was made at the tip of the ventricular catheter, (b) the system was kept filled with heparinized saline, (c) cooled saline was injected by a senior member of the team with meticulous attention to eliminate bubbles, and (d) each study was under the constant supervision of a senior member of the study team. Strain gauge transducers were positioned at the level of the fourth intercostal space 5 cm posterior to the "angle of Lewis." Left ventricular ejection time (LVET) was measured from the "external carotid pulse tracing." Weissler, Peeler, and Roehll (28) have shown this method of measuring the duration of left ventricular ejection to be nearly identical with that measured from the undamped curves obtained through fluid-filled catheters positioned in the aortic roots of five resting subjects. This has been confirmed by Whittaker, Shaver, Gray, and Leonard (29), who compared measurements from external carotid pulse tracings with those recorded simultaneously from the central aortic pulse obtained with a catheter tip manometer. The latter authors showed the variations in ejection periods measured by the two methods to be practically identical in response to methoxamine and amyl nitrite. More recently, Bush, Lewis, Leighton, Fontana, and Weissler (30) have shown that systolic time intervals measured by the noninvasive external method and with catheter tip manometers are practically identical. In our study, measurements for each state were made over a period of approximately 5 min and, wherever possible, in random order

<sup>3</sup> Specially prepared by Victory Engineering Corp., Springfield N. J., model AX-1212A.

to minimize systematic error. Observations were made under control conditions, with subjects in the supine posture, and in the 60° head-up tilted position, and were then repeated in the same positions during I infusion (1-1.5 µg/min). No more than 150 cc of blood was withdrawn for study during the procedure. Recordings were made on an Electronics for Medicine, Inc. (White Plains, N. Y.) multichannel oscilloscopic research recorder. Each subject served as his own control, and statistics were calculated utilizing the *t* test for paired variates (31).

## CALCULATIONS

To obtain left ventricular circumference, ventricular wall forces during ejection, and MRCS, calculations were made, assuming that the left ventricle behaves as a contracting thin-walled sphere. Ross, Covell, Sonnenblick, and Braunwald (10), assuming the intact left ventricle of the dog to be spherical, have shown that the shape of the basic force-velocity relationship and its alteration by inotropic influences are not affected by the method used for calculating tension. Consequently, the spherical model has been utilized as a logical basis for the calculation of indices of ventricular wall force and velocity of shortening in this study. It is emphasized that values derived in this manner should be regarded as reasonable indices rather than absolute values. LVEDV and LVESV were calculated from the ratio of ESV to EDV (obtained from thermodilution curves) and from the stroke volume (23, 25, 32). Although the validity of the indicator dilution method of determining left ventricular volume has been questioned (33, 34), Hugenholtz, Wagner, and Sandler (35) have shown a close correlation between values for LVEDV derived from fiberoptic indicator dilution and from left ventriculography. Although volumes obtained by the former method were systematically somewhat larger than those obtained by the radiographic technique, those investigators found that the relationship of values of LVEDV obtained by the two methods remains consistent regardless of ventricular size, stroke volume, or heart rate. Carleton, Bowyer, and Graettinger (36), while noting a similar systematic discrepancy between values obtained by the two methods, have observed that indicator dilution is useful in providing an index of left ventricular volume as well as of variations therein. Frank and Levinson (14) have also concluded that indicator dilution provides reliable measurements of end-diastolic volume in the normal left ventricle, especially for purposes of assessing changes induced by various interventions.

From the ventricular volumes, end-diastolic circumference (LVEDC) and end-systolic circumference (LVESC) were calculated. The difference between the circumferences, i.e. the magnitude of circumferential shortening ( $\Delta C$ ) during left ventricular ejection, was

divided by the duration of left ventricular ejection (LVET) to obtain MRCS.

$$\Delta C = \text{LVEDC} - \text{LVESC} \text{ centimeters.}$$

$$\text{MRCS} = \frac{\Delta C}{\text{LVET}} \text{ centimeters per second.}$$

Ventricular wall tension was calculated for a thin-walled sphere as the product of the force per unit circumference (Pressure  $\times$  Radius/2) and the circumference ( $2 \pi \times$  Radius) and is expressed as that force acting perpendicular to the radius of the ventricle in grams. Thus,

$$F = Pr/2 \times 2\pi r \times \frac{13.6}{10} = P\pi r^2 \times \frac{13.6}{10}$$

where *P* is the pressure in millimeters of Hg and *r* is the radius in centimeters.

Accordingly, force at the onset of ejection,

$$F_{OE} = P_{OE}\pi r_{OE}^2 \times \frac{13.6}{10},$$

was calculated as the product of the radius of the ventricle at the onset of ejection and the aortic end-diastolic pressure (that pressure acting on the ventricular wall at the onset of ejection). The force at the end of ejection,

$$F_{EE} = P_{EE}\pi r_{EE}^2 \times \frac{13.6}{10},$$

was derived as the product of the end-systolic radius and the aortic pressure at the instant of aortic valve closure. The difference between  $F_{OE}$  and  $F_{EE}$  in this study averaged about 10% of  $F_{OE}$  and never exceeded 25%. It has been predicted that the ejection phase of contraction of the normal left ventricle is not strictly isotonic and that the force in the left ventricular wall should fall during ejection (37). Moreover, there is evidence in dogs demonstrating a peak force early during ejection followed by a decline which is slight relative to the peak force (38). A similar linear fall in ventricular wall tension was observed in the normal human heart by Gault, Ross, and Braunwald (39), though in that study the magnitude of force decrement was relatively large. Mean force during ejection was, therefore, calculated in this study as

$$\text{MFE} = \frac{F_{OE} + F_{EE}}{2}.$$

This expression of ventricular wall tension was chosen to represent "circumferential load" during ejection to correspond with "total load" in afterloaded contraction of the isolated papillary muscle.

Stroke work (SW) was calculated as the product of mean arterial pressure, in millimeters of Hg, and stroke volume, in cubic centimeters, and was corrected to be expressed in gram meters.

$$\left\{ \begin{aligned} SW &= MAP \times SV \times \frac{13.6}{1000} \end{aligned} \right.$$

The quotient of stroke work and LVET yielded stroke power (SP),

$$SP = \frac{SW}{LVET} \text{ gram meters per second.}$$

Mean rate of left ventricular ejection (MRLVE) was calculated by the quotient,

$$MRLVE = \frac{SV}{LVET} \text{ cubic centimeters per second.}$$

## RESULTS

The results in each of the five subjects studied are shown in Table I, with statistical statements in Table II. Mean values are expressed as  $\pm$ SEM.

## Control state

*Effect of posture change on left ventricular end-diastolic volume, left ventricular end-systolic volume, stroke volume, and ejection fraction (Fig. 1).* In each of the five subjects studied, LVEDV diminished in the 60° head-up tilted posture as compared with the supine. The reduction ranged from 21 to 38% with a mean reduction of  $29 \pm 3\%$  ( $P < 0.01$ ). There was an associated reduction of LVESV in each case, ranging from 20 to 36% of supine values with a mean reduction of  $25 \pm 3\%$  ( $P < 0.01$ ), and a fall in stroke volume which varied from 23 to 41% of supine values with a mean drop of  $34 \pm 3\%$  ( $P < 0.01$ ). The ejection fraction (SV/LVEDV) decreased slightly on assumption of the tilted posture ( $-7 \pm 2\%$ ,  $P < 0.05$ ).

*Effect of posture change on arterial blood pressure and mean force of ejection.* Although LVEDV diminished, there were no significant changes in AESP, AEDP, peak ASP, or MAP between the two positions. As a consequence, in accordance with the LaPlace principle, there was a fall in MFE ( $-17 \pm 2\%$ ,  $P < 0.01$ ) associ-

TABLE I  
Summary of Measured and Derived

Subject	MAP	Peak	AEDP	AESP	LVET	CO	CI	HR	$\frac{T}{T-1}$	LVSV	
		ASP							$(T-1)$		
	mm Hg	mm Hg	mm Hg	mm Hg	sec	liters/min	liters/ min per m <sup>2</sup>	beats/ min		cm <sup>3</sup>	
C. D.	(CS)	93	120	70	96	0.373	6.10	2.96	56	0.55	109
	(CT)	89	120	71	98	0.283	5.05	2.45	60	0.56	84
	(IS)	92	179	72	96	0.281	10.44	5.07	72	0.41	145
	(IT)	96	198	79	109	0.245	9.10	4.42	100	0.45	91
M. J.	(CS)	86	119	73	93	0.270	6.54	3.07	80	0.55	82
	(CT)	94	119	80	98	0.229	5.00	2.34	88	0.56	57
	(IS)	92	132	72	94	0.231	8.97	4.21	96	0.50	93
	(IT)	97	131	78	94	0.179	7.54	3.54	116	0.50	65
J. H.	(CS)	81	112	65	87	0.331	4.92	2.22	52	0.58	95
	(CT)	81	109	62	88	0.244	4.24	1.89	75	0.64	57
	(IS)	91	129	66	93	0.261	8.90	3.97	73	0.45	122
	(IT)	81	121	67	74	0.197	6.13	2.73	100	0.51	61
F. T.	(CS)	113	144	89	109	0.311	5.00	2.59	74	0.56	68
	(CT)	109	144	91	111	0.222	4.33	2.24	98	0.61	44
	(IS)	103	167	87	91	0.188	8.92	4.62	130	0.52	69
	(IT)	103	160	84	80	0.160	5.14	2.66	154	0.52	33
D. S.	(CS)	89	122	67	88	0.296	5.23	3.08	74	0.56	71
	(CT)	84	107	75	84	0.221	4.16	2.45	98	0.58	42
	(IS)	84	123	65	83	0.255	7.73	4.55	87	0.44	89
	(IT)	85	113	65	69	0.182	5.18	3.05	129	0.44	40
Average	(CS)	92 $\pm$ 6	123 $\pm$ 5	73 $\pm$ 4	95 $\pm$ 4	0.316 $\pm$ 0.017	5.56 $\pm$ 0.32	2.78 $\pm$ 0.17	67 $\pm$ 6	0.56 $\pm$ 0.01	85 $\pm$ 8
	(CT)	91 $\pm$ 5	120 $\pm$ 7	76 $\pm$ 5	96 $\pm$ 5	0.240 $\pm$ 0.012	4.56 $\pm$ 0.19	2.27 $\pm$ 0.10	84 $\pm$ 7	0.59 $\pm$ 0.02	57 $\pm$ 7
	(IS)	92 $\pm$ 3	146 $\pm$ 11	72 $\pm$ 4	91 $\pm$ 2	0.243 $\pm$ 0.016	8.99 $\pm$ 0.43	4.48 $\pm$ 0.19	92 $\pm$ 11	0.46 $\pm$ 0.02	104 $\pm$ 13
	(IT)	92 $\pm$ 4	145 $\pm$ 16	75 $\pm$ 4	85 $\pm$ 7	0.193 $\pm$ 0.014	6.62 $\pm$ 0.76	3.28 $\pm$ 0.32	120 $\pm$ 10	0.48 $\pm$ 0.02	58 $\pm$ 10

CS, control supine; CT, control tilt; IS, isoproterenol supine; IT, isoproterenol tilt; MAP, peak ASP, AEDP, and AESP, mean, peak, end-diastolic, and end-systolic aortic pressures, respectively; LVET, left ventricular ejection time; CO and CI, cardiac output and index, respectively; HR, heart rate;  $\frac{T}{T-1}$ , thermal ratio of LVESV/LVEDV; LVSV, stroke volume; LVSV/LVEDV, ejection fraction; LVEDV and LVESV, left ventricular end-diastolic and end-systolic volumes, respectively; LVEDC, left ventricular end-diastolic circumference;  $\Delta C$ , circumferential change during ejection; MRCS, mean rate of circumferential shortening; MRLVE, mean rate of left ventricular ejection; SW, SP, stroke work and power, respectively; F<sub>0E</sub>, F<sub>EE</sub>, MFE, ventricular wall force at onset and end of ejection and mean force of ejection, respectively.

ated with the reduction of left ventricular volume in the tilted posture (Fig. 1 D).

*Effect of posture change on mean rate of circumferential shortening, mean rate of left ventricular ejection, stroke work, and stroke power.* In the supine position, MRCS averaged  $12.5 \pm 0.6$  cm/sec, ranging from 11.6 to 14.8 cm/sec. In the tilted position, it averaged  $13.3 \pm 0.5$  cm/sec, ranging from 11.9 to 14.8 cm/sec. Thus, the MRCS of each subject in the two positions showed no significant differences (Fig. 1 E). The constancy of MRCS over the broad range of LVEDV and MFE observed in the study is shown in Fig. 2. On the other hand, there was a fall in MRLVE ( $-13 \pm 4\%$ ,  $P < 0.05$ ), SW ( $-34 \pm 4\%$ ,  $P < 0.01$ ), and SP ( $-14 \pm 4\%$ ,  $P < 0.05$ ) in consequence of the reduction of SV in the tilted posture as compared with the supine. The relationship of each of these extracardial parameters to LVEDV is shown in Fig. 3.

### During isoproterenol infusion

*Effect of isoproterenol on left ventricular end-diastolic volume, left ventricular end-systolic volume, stroke vol-*

*ume, and ejection fraction (Fig. 1).* In the supine posture during I infusion LVEDV was practically unchanged from that in the control supine position in four subjects (C. D. +2%, M. J. +2%, J. H. -2%, D. S. -1%) and fell slightly in one (F. T. -7%). However, LVESV declined in all subjects ( $-18 \pm 3\%$ ,  $P < 0.01$ ). This encroachment on LVESV reserve accounted for a marked increase in SV in four subjects (C. D. 33%, M. J. 13%, J. H. 28%, D. S. 25%), with essentially no change in one (F. T. +1%) in whom I caused the most pronounced increase in heart rate (76%). The ejection fraction was increased in all subjects ( $22 \pm 5\%$ ,  $P < 0.02$ ).

In the head-up tilted posture during I infusion, there was a significant decrease of LVEDV ( $-21 \pm 7\%$ ,  $P < 0.05$ ) and LVESV ( $-35 \pm 7\%$ ,  $P < 0.01$ ) from that in the control tilted position. SV in the tilted posture during I infusion was not significantly different from that observed in the control tilted position. In all subjects, the ejection fraction in the tilted posture during I infusion was greater than that observed in either of the postures without I and was approximately the same as in the supine position with I.

### Data for Each Subject

LVSU/ LVEDV	LVEDV	LVESV	LVEDC	$\Delta C$	MRCS	MRLVE	SW	SP	F <sub>OE</sub>	F <sub>EE</sub>	MFE
	cm <sup>3</sup>	cm <sup>3</sup>	cm	cm	cm/sec	cm <sup>3</sup> /sec	g m	g m/sec	gf	gf	gf
0.45	242	133	24.3	4.4	11.8	292	138	370	4470	4110	4290
0.44	191	107	22.4	3.9	13.8	297	102	359	3860	3630	3740
0.59	246	101	24.4	6.3	22.4	516	181	646	4640	3400	4020
0.55	165	74	21.4	5.0	20.4	371	119	485	3920	3170	3540
0.45	182	100	22.1	4.0	14.8	304	96	355	3860	3300	3580
0.44	130	73	19.7	3.4	14.8	249	73	318	3360	2820	3090
0.50	186	93	22.2	4.6	19.9	403	116	504	3840	3150	3500
0.50	130	65	19.7	4.0	22.3	363	86	479	3280	2480	2880
0.42	226	131	23.7	3.9	11.8	287	105	316	3950	3690	3820
0.36	158	101	21.1	2.9	11.9	234	63	257	2990	3150	3070
0.55	222	100	23.6	5.5	21.1	467	151	578	4000	3300	3650
0.49	124	63	19.4	3.9	19.8	310	67	341	2730	1920	2320
0.44	155	87	20.9	3.6	11.6	219	105	336	4210	3520	3860
0.39	113	69	18.8	2.8	12.6	198	65	294	3480	3080	3280
0.48	144	75	20.4	4.0	21.3	367	97	514	3920	2650	3280
0.48	69	36	16.0	3.1	19.4	206	46	289	2330	1440	1880
0.44	161	90	21.2	3.7	12.5	240	86	290	3260	2920	3090
0.42	100	58	18.1	3.0	13.6	190	48	217	2660	2070	2360
0.56	159	70	21.1	5.0	19.6	349	102	399	3130	2330	2730
0.56	71	31	16.1	3.9	21.4	220	46	254	1820	1110	1460
0.44 ±0.01	193 ±17	108 ±10	22.4 ±0.7	3.9 ±0.1	12.5 ±0.6	268 ±16	106 ±9	333 ±14	3950 ±200	3510 ±200	3730 ±200
0.41 ±0.02	138 ±16	82 ±10	20.0 ±0.8	3.2 ±0.2	13.3 ±0.5	234 ±19	70 ±9	289 ±24	3270 ±210	2950 ±260	3110 ±220
0.54 ±0.02	191 ±19	88 ±6	22.3 ±0.7	5.1 ±0.4	20.9 ±0.5	420 ±31	129 ±16	528 ±41	3910 ±240	2970 ±200	3440 ±210
0.52 ±0.02	112 ±18	54 ±9	18.5 ±1.1	4.0 ±0.3	20.7 ±0.5	294 ±35	73 ±14	370 ±48	2820 ±370	2020 ±370	2420 ±370

TABLE II  
Statistical Analyses

	Control tilt vs. control supine (STD)	I tilt vs. I supine (STD)	I supine vs. control supine (STD)	I tilt vs. control tilt (STD)
LVEDV	-29 ±3% ( <i>P</i> < 0.01)	-43 ±5% ( <i>P</i> < 0.01)	-1 ±2%	-21 ±7% ( <i>P</i> < 0.05)
LVESV	-25 ±3% ( <i>P</i> < 0.01)	-40 ±6% ( <i>P</i> < 0.01)	-18 ±3% ( <i>P</i> < 0.01)	-35 ±7% ( <i>P</i> < 0.01)
LVSV	-34 ±3% ( <i>P</i> < 0.01)	-45 ±5% ( <i>P</i> < 0.01)	+20 ±6% ( <i>P</i> < 0.05)	0 ±7%
LVSV/LVEDV	-7 ±2% ( <i>P</i> < 0.05)	-4 ±2%	+22 ±5% ( <i>P</i> < 0.02)	+26 ±4% ( <i>P</i> < 0.01)
MRLVE	-13 ±4% ( <i>P</i> < 0.05)	-31 ±6% ( <i>P</i> < 0.01)	+37 ±8% ( <i>P</i> < 0.01)	+25 ±7% ( <i>P</i> < 0.05)
SW	-34 ±4% ( <i>P</i> < 0.01)	-45 ±6% ( <i>P</i> < 0.01)	+21 ±9%	+2 ±9%
SP	-14 ±4% ( <i>P</i> < 0.05)	-30 ±7% ( <i>P</i> < 0.02)	+59 ±9% ( <i>P</i> < 0.01)	+28 ±9% ( <i>P</i> < 0.05)
MAP	-1 ±3%	-1 ±3%	+1 ±4%	+1 ±2%
Peak ASP	-3 ±2%	-2 ±3%	+18 ±8%	+21 ±11%
AEDP	+4 ±3%	+3 ±2%	0 ±1%	-1 ±5%
AESP	+1 ±2%	-7 ±6%	-3 ±4%	-11 ±7%
F <sub>OE</sub>	-17 ±2% ( <i>P</i> < 0.01)	-29 ±6% ( <i>P</i> < 0.01)	-1 ±2%	-17 ±7%
F <sub>EE</sub>	-17 ±3% ( <i>P</i> < 0.01)	-34 ±8% ( <i>P</i> < 0.02)	-15 ±3% ( <i>P</i> < 0.01)	-33 ±9% ( <i>P</i> < 0.05)
MFE	-17 ±2% ( <i>P</i> < 0.01)	-31 ±7% ( <i>P</i> < 0.02)	-8 ±2% ( <i>P</i> < 0.02)	-23 ±8% ( <i>P</i> < 0.05)
MRCS	+7 ±3%	-1 ±5%	+69 ±10% ( <i>P</i> < 0.01)	+55 ±3% ( <i>P</i> < 0.01)

Abbreviations as in Table I.

Effect of isoproterenol on arterial blood pressure and mean force of ejection. MAP, AEDP, and AESP were practically no different during I infusion in both the supine and tilted postures from the values observed in the same positions without I. Peak ASP tended to be higher during I infusion in both postures but not significantly so. MFE declined during I infusion in both the supine ( $-8 \pm 2\%$ ,  $P < 0.02$ ) and tilted ( $-23 \pm 8\%$ ,  $P < 0.05$ ) postures (Fig. 1).

Effect of isoproterenol on mean rate of circumferential shortening, mean rate of left ventricular ejection, stroke work, and stroke power. MRCS increased markedly during I infusion in both the supine ( $69 \pm 10\%$ ,  $P < 0.01$ ) and tilted postures ( $55 \pm 3\%$ ,  $P < 0.01$ ). As in the control state, there was a constancy of MRCS at the increased value over the entire range of LVEDV and MFE observed in the two positions (Fig. 2).

In the supine posture during I infusion, there was an increase in MRLVE ( $57 \pm 8\%$ ,  $P < 0.01$ ) and SP ( $59 \pm 9\%$ ,  $P < 0.01$ ). SW increased in four subjects (C. D., M. J., J. H., and D. S.) but decreased in the fifth (F. T.) in whom a marked tachycardia was associated with a drop of SV during I infusion. Compared with the control tilted posture, MRLVE in the tilted posture during I infusion increased significantly ( $25 \pm 7\%$ ,  $P < 0.05$ ). SP also showed a significant increase ( $28 \pm 9\%$ ,  $P < 0.05$ ), but there was no significant difference in SW. Fig. 3 shows the volume dependency of MRLVE, SP, and SW.

## DISCUSSION

Left ventricular volume, stroke volume, and cardiac output. The hemodynamic effects of upright posture in

man have been studied in detail, and several investigators have shown that assumption of the upright position results in a decrease of cardiac output and stroke volume (40-48). In addition, it has been demonstrated that a reduction of heart size, measured from chest roentgenograms, occurs in normal subjects in the sitting posture as compared with the supine (49-51). Recently, Rapaport, Wong, Escobar, and Martinez (52) have shown a diminution of right ventricular end-diastolic volume when patients without congestive heart failure were tilted to the 60° upright position.

In the present study, when subjects were changed from the supine to the tilted posture, LVEDV became considerably smaller with a concomitant reduction of cardiac output and stroke volume, both in the control state and during steady-state response to I. The left ventricular stroke fraction was greater during I infusion in both postures; however, a change of posture from supine to head-up tilt resulted in a greater reduction of LVEDV with I than without. This is compatible with the higher heart rate during I but may also indicate exaggerated vascular "pooling" due to gravitational influences associated with infusion with I (53). There was little variation of LVEDV in response to I when subjects were supine. Only one (F. T.) exhibited a smaller LVEDV during I infusion, and in that subject the associated heart rate response was greater than twice the average of the other four subjects. This finding differs from that of Harrison, Glick, Goldblatt, and Braunwald (54), who have reported that external ventricular wall dimensions decreased when I was infused into patients in whom metal clips had been sewn to the epicardial surface at the time of cardiac surgery. Changes in distance between

the clips observed by cineradiography were interpreted to indicate ventricular chamber size reduction. Our finding was further confirmed by a recent study in our laboratory which has shown a slight random variation of LVEDV, determined by cineventriculography, in response to I in subjects in the supine posture (55). Thus, LVEDV does not appear to be characteristically reduced in normal subjects during response to I in the supine posture.

*Relation of MRCS to left ventricular volume and myocardial wall forces.* The concept of MRCS as applied in this study is based on the assumption that this parameter reflects, as an index, the integral of the velocity of shortening of all left ventricular myocardial fibers over the duration of ejection. The subjects of the investigation were normal young men without evidence of heart disease, thus ruling out influences of myocardial and valvular abnormalities. MRCS is considered analogous to the velocity of isotonic shortening observed in studies of isolated papillary muscle, although in the latter, velocity of fiber shortening has been measured from the slope of the initial most rapid portion of the time-distance curve (1, 4, 7); however, analysis of such curves from the work of Sonnenblick (2) demonstrates that the mean rate of shortening of an isolated papillary muscle segment bears a highly significant linear relationship to the velocity of shortening measured from the initial slope. It is evident from the data in a left ventriculographic study carried out by Gault et al. (39) that the relationship between maximum velocity and mean velocity of shortening of the midventricular circumference is similar in vivo to that observed in isolated cardiac muscle.

It has been shown that in the heart of the normal dog (38) and of man (39), ventricular wall tension during systole falls in a nearly-linear fashion after development of peak force early in the ejection phase. Therefore, ventricular wall force in this study is represented as a mean tension during ejection, MFE. This method of calculation probably underestimates the true mean force of ejection, but the error is considered small and would tend to be consistent in each subject of this study. Consequently, MFE is utilized as an index of systolic left ventricular wall tension and with MRCS is used to construct the mean force-velocity relationship of the intact left ventricle.

This study shows a fall of MFE as a result of a reduction of ventricular volume in the upright posture as compared with supine (Fig. 1 A, B, D). However, MRCS remained constant over the entire ranges of MFE and LVEDV observed in the two positions (Fig. 2). When a positive inotropic intervention, I, was imposed, MRCS increased markedly over that of the control state, but as in the latter, remained constant (at the increased level) over a similar range of left ventricular size and

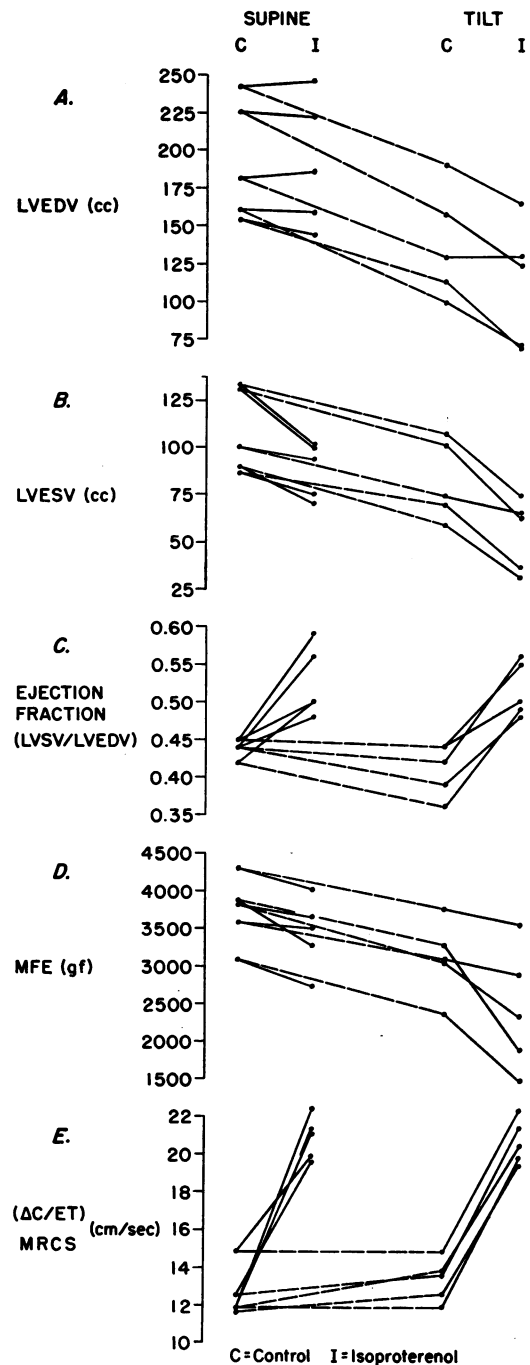


FIGURE 1 Panels A-E show the individual responses for left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), ejection fraction, mean force of ejection (MFE), and mean rate of circumferential shortening (MRCS). For explanation, see text.

MFE. This observation was unexpected in the light of the form of the force-velocity relationship observed in in vitro studies of isolated papillary muscle preparations

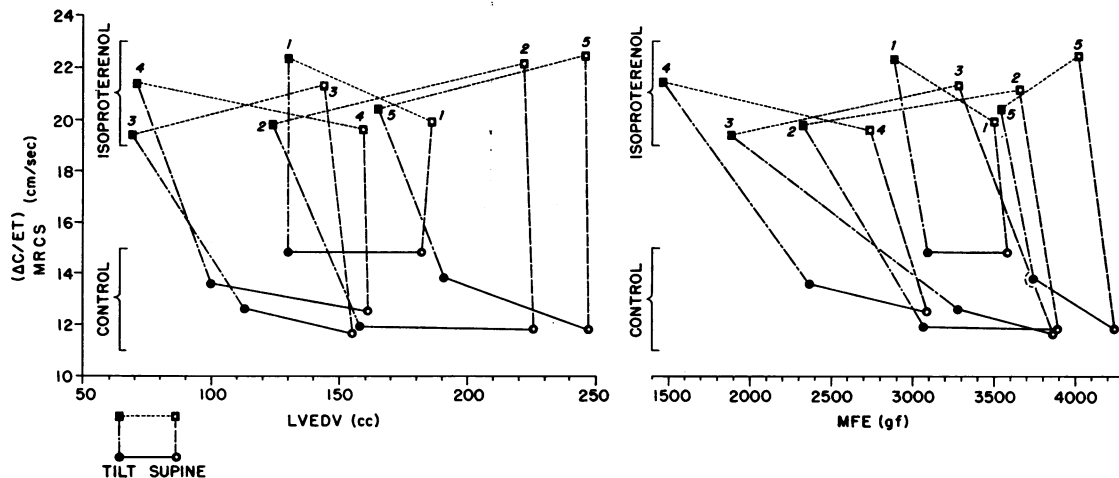


FIGURE 2 The values for mean rate of circumferential shortening (MRCS) in each subject in the control state and during isoproterenol infusion in both the supine and tilted postures. Open circles represent supine controls, closed circles represent tilted controls; the two are connected by a solid line. Open squares represent supine posture during I infusion, closed squares represent the tilted posture during I infusion; the two are connected with a dotted line. The two supine postures are connected with a dashed line (---) and the two tilted postures with a broken line (- · - · -). LVEDV, left ventricular end-diastolic volume; MFE, mean force of ejection. Note the two levels of MRCS, both constant over the broad range of LVEDV and MFE.

in which the influences of force and initial length of contraction are uncoupled and can be studied separately. In such preparations it has been demonstrated that there is an inverse relationship between force (load) and velocity of shortening (1-6). Thus, as load is decreased, the velocity of shortening increases. Consequently, in the present study, applying the force-velocity principle alone, it was anticipated that a reduction of ventricular wall force associated with the head-up tilted posture would be associated with an increase of MRCS. However, as alluded to above, while MRCS increased in response to I, it remained constant over the ranges of LVEDV and MFE induced by changes of posture. These observations indicate that in the normal intact heart, while an increase in myocardial contractility is associated with an increase in the velocity of ventricular wall shortening during ejection, the effect of variations of ventricular wall force associated with changes of ventricular volume is somehow nullified.

It has been demonstrated in the isolated muscle preparation that initial muscle length is an independent determinant of velocity of shortening (1-5). In other words, without a change of myocardial contractility, an increase in initial muscle length shifts the force-velocity relationship to the right and upward, and, conversely, a decrease in initial muscle length slows the velocity of shortening. In the intact left ventricle, unlike the isolated papillary muscle preparation, the influences of myocardial wall force and of initial muscle length on

velocity of shortening during ejection are coupled. Thus, as the heart varies in end-diastolic volume, not only does the ventricular wall force of ejection vary in accordance with the LaPlace concept (56), but the initial myocardial fiber length of the ventricular wall varies as well. In the normal heart, and probably in all hearts operating on the ascending limb of a ventricular function curve, each of these two factors, MFE and LVEDV, acts in an opposite way in its effect on the velocity of left ventricular wall shortening, thus tending to maintain a constancy of MRCS independent of ventricular chamber volume.

This concept of the reciprocal effects of the coupled influences of force and volume in the intact heart is supported by the observations of Levine and Britman (9), Sonnenblick (5), and Fry, Griggs, and Greenfield (8), the latter of whom concluded, "first, that there is a reciprocal relationship between the tension in the muscle and the velocity with which it is shortening at any instantaneous volume, and, second, for any instantaneous tensions, the velocity of shortening increases with increased heart volume." Ross et al. (10) have reached a similar conclusion in a study of variably afterloaded and isovolumic left ventricular conditions in dogs. In addition, examination of the family of force-velocity curves, which are produced by variations in initial length of contraction in the isolated papillary muscle preparation, indicates that for a given state of contractility there are ranges of both length and load through which appropriate adjust-



ments of these two factors can yield constant velocities of shortening (2, 4, 5). Thus, in the intact normal heart, it is reasonable to anticipate a tendency toward a constancy of MRCS for any given state of myocardial contractility. In this respect, MRCS as an index of myocardial contractility is similar to the theoretical value for maximal velocity of shortening of the contractile element of the isovolumically contracting ventricle ( $V_{max}$ ) which has been shown to be constant for any given state of myocardial contractility independent of ventricular wall force and volume (15).

It has been demonstrated that the rate of left ventricular wall shortening during systole is in part dependent on the peripheral vascular impedance structure (10, 57, 58). Thus, it is possible that the increase of MRCS in response to I observed in this study was in part due to diminished MFE. However, the constancy of MRCS in the two postures during I infusion over the broad range of MFE observed in this investigation indicates that the relative effect of diminished peripheral vascular impedance was the same in both positions. This is also suggested by the tendency for the ejection fraction to maintain a constant value characteristic of each of the inotropic states in the two postures, indicating that variations in ventricular filling and the consequent effects upon stroke volume are accompanied by matching adjustments in peripheral vascular impedance structure. Because the ejection fraction appears to have a characteristic value for any given inotropic state over a relatively broad range of ventricular-loading conditions, it has been suggested as an index of myocardial contractility (59-65). The slight reduction of ejection fraction in the control tilted posture observed in this study suggests the possibility of a physical limit to which the ventricular wall can shorten. A similar tendency during I infusion was not statistically significant in this study. MRCS thus appears to represent an index of myocardial contractility which is independent of variations of ventricular size and wall tension. However, the possibility that significant increases in afterload above normal levels may cause a decrease in MRCS without a decrease in myocardial contractility is suggested by: (a) Shaver, Kroetz, Leonard, and Paley (66) have shown an increase in systolic ejection time associated with an increase of LVEDP in patients receiving methoxamine infusion while heart rate was kept constant by atrial pacing, indicating a reduction of MRCS at an increased LVEDV, and (b) Mason, Spann, and Zelis (16) have shown a relatively small increase in  $V_{max}$  during methoxamine infusion, indicating that methoxamine does not much change myocardial contractility.

*Relation of MRCS to heart rate.* In this study, whereas MRCS increased markedly in response to the positive inotropic effect of isoproterenol, variations of

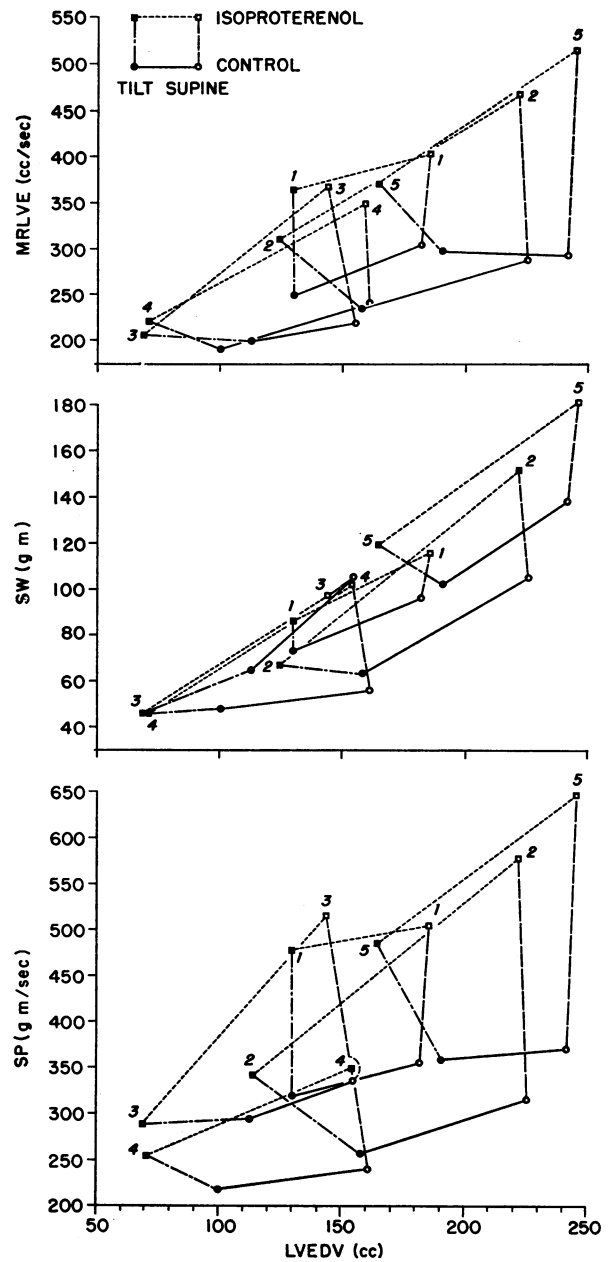


FIGURE 3 Mean rate of left ventricular ejection (MRLVE), stroke work (SW), and stroke power (SP) in relation to left ventricular end-diastolic volume (LVEDV). Note the volume dependency of these three parameters. MRLVE and SP more clearly differentiate the two states of myocardial contractility (control and isoproterenol) than does SW.

heart rate associated with changes in posture had a small and variable effect on the mean velocity of left ventricular shortening. In the control state, of the three subjects whose heart rates increased substantially in response to the head-up tilted posture, two showed a slight increase in MRCS (F. T., D. S.) and one had no

change (J. H.). In the other two subjects who had practically no change in heart rate when posture was changed, one showed a slight increase in MRCS (C. D.) and the other showed no change (M. J.). During isoproterenol infusion, increases in heart rate due to change in posture varied from 20 to 42 beats/min. The associated variations in MRCS were relatively small and inconsistent, two showing a slight increase (M. J., D. S.) and three showing a slight decrease (C. D., J. H., F. T.). A number of investigators have described an augmentation in the velocity of shortening of isolated mammalian cardiac muscle in response to increases of rate of contraction, especially at rates below 60/min (1-4, 57, 58, 67). At higher rates, increasing contraction frequency causes little change or may decrease force of contraction and velocity of shortening. In the intact areflexic dog heart, Mitchell, Wallace, and Skinner (68) have shown those hemodynamic variables which reflect the speed of myocardial contraction to be increased by augmentation of heart rate. Covell, Ross, Taylor, Sonnenblick, and Braunwald (12), in a study in dogs, have shown an increase in isovolumic contractile element-shortening velocity and in force of contraction associated with increases of heart rate. In both of the latter investigations, (a) increments of heart rate as well as the absolute levels of heart rate from which those increments were induced were considerably greater than those observed in the control state of our investigation, and (b) magnitude of increases of velocity of ventricular wall shortening were relatively small. Sonnenblick, Morrow, and Williams (69) in a study in patients during cardiac operations found no augmentation in the magnitude but a moderate increase in the rate of force development of a constant length of right ventricular wall in response to relatively large increases of heart rate. In another study, Sonnenblick, Braunwald, Williams, and Glick (70) showed in man that doubling the heart rate from normal resting levels by atrial pacing significantly increased velocity of myocardial wall shortening. The method involved measurement of the length-time slope of the distance between metal clips sewn to the right ventricle during prior cardiac surgical procedures. Measurements were made at isolength points in each condition of the study, while associated pressure changes in the right ventricle were small and inconstant. Though the present study was not designed to investigate the effect of heart rate alone on MRCS, it is apparent from the data that changes of MRCS associated with changes of heart rate observed in this study were small and variable. Additional studies are being performed to clarify the effect of heart rate on MRCS.

*Comparison of MRCS with volume-dependent parameters of left ventricular performance (SW, SP, MRLVE).* The volume-dependent parameters of left

ventricular performance have been utilized by several investigators (71-73). When LVEDV and blood pressure can be controlled, SW, SP, and MRLVE represent useful indications of the velocity of left ventricular wall contraction. However, in the present study in which it was impractical to control LVEDV and blood pressure, the volume-dependent parameters are only partially effective in differentiating the changes associated with the inotropic state induced by I. Consequently, while the values for SW, SP, and MRLVE are widely different in the two states of left ventricular myocardial contractility at the larger LVEDV observed in this study, they converge at smaller heart sizes, thereby obscuring the inotropic differences (Fig. 3). On the other hand, the values for MRCS in the control state are widely separated from those seen during response to I over the entire range of LVEDV and MFE observed in this study (Fig. 2). This clearly demonstrates the usefulness of MRCS as an independent index of left ventricular myocardial contractility under the conditions of this investigation.

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#### REFERENCES

1. Abbott, B. C., and W. F. H. M. Mommaerts. 1959. A study of inotropic mechanisms in the papillary muscle preparation. *J. Gen. Physiol.* **42**: 533.
2. Sonnenblick, E. H. 1962. Force-velocity relations in mammalian heart muscle. *Amer. J. Physiol.* **202**: 931.
3. Sonnenblick, E. H. 1962. Implications of muscle mechanics in the heart. *Fed. Proc.* **21**: 975.
4. Sonnenblick, E. H., E. Braunwald, and A. G. Morrow. 1965. The contractile properties of human heart muscle: studies on myocardial mechanics of surgically excised papillary muscles. *J. Clin. Invest.* **44**: 966.
5. Sonnenblick, E. H. 1965. Instantaneous force-velocity-length determinants in the contraction of heart muscle. *Circ. Res.* **16**: 441.
6. Hill, A. V. 1938. The heat of shortening and the dynamic constants of muscle. *Proc. Roy. Soc. Ser. B Biol. Sci.* **126**: 136.
7. Abbott, B. C., and D. R. Wilkie. 1953. The relation between velocity of shortening and the tension-length curve of skeletal muscle. *J. Physiol. (London)*. **120**: 214.
8. Fry, D. L., D. M. Griggs, Jr., and J. C. Greenfield, Jr. 1964. Myocardial mechanics: tension-velocity-length relationships of heart muscle. *Circ. Res.* **14**: 73.
9. Levine, H. J., and N. A. Britman. 1964. Force-velocity relations in the intact dog heart. *J. Clin. Invest.* **43**: 1383.
10. Ross, J., Jr., J. W. Covell, E. H. Sonnenblick, and E. Braunwald. 1966. Contractile state of the heart characterized by force-velocity relations in variably after-loaded and isovolumic beats. *Circ. Res.* **18**: 149.

11. Covell, J. W., J. Ross, Jr., E. H. Sonnenblick, and E. Braunwald. 1966. Comparison of the force-velocity relation and the ventricular function curve as measures of the contractile state of the intact heart. *Circ. Res.* 19: 364.
12. Covell, J. W., J. Ross, Jr., R. Taylor, E. H. Sonnenblick, and E. Braunwald. 1967. Effects of increasing frequency of contraction on the force velocity relation of left ventricle. *Cardiovasc. Res.* 1: 2.
13. Gleason, W. L., and E. Braunwald. 1962. Studies on the first derivative of the ventricular pressure pulse in man. *J. Clin. Invest.* 41: 80.
14. Frank, M. J., and G. E. Levinson. 1968. An index of the contractile state of the myocardium in man. *J. Clin. Invest.* 47: 1615.
15. Mason, D. T. 1969. Usefulness and limitations of the rate of rise of intraventricular pressure (dp/dt) in the evaluation of myocardial contractility in man. *Amer. J. Cardiol.* 23: 516.
16. Mason, D. T., J. F. Spann, Jr., and R. Zelis. 1970. Quantification of the contractile state of the intact human heart. *Amer. J. Cardiol.* 26: 248.
17. Siegel, J. H., and E. H. Sonnenblick. 1963. Isometric time-tension relationships as an index of myocardial contractility. *Circ. Res.* 12: 597.
18. Paley, H. W., A. M. Weissler, and C. D. Schoenfeld. 1964. The effect of upright posture on left ventricular volume in man. *Clin. Res.* 12: 105. (Abstr.)
19. Paley, H. W., I. G. McDonald, and A. M. Weissler. 1964. The relationship of left ventricular circumferential contraction to left ventricular ejection time as an inotropic index in man. *Clin. Res.* 12: 191. (Abstr.)
20. Gorlin, R., E. L. Rolett, P. M. Yurchak, and W. C. Elliott. 1964. Left ventricular volume in man measured by thermodilution. *J. Clin. Invest.* 43: 1203.
21. Gault, J. H., J. W. Covell, E. Braunwald, and J. Ross. 1970. Left ventricular performance following correction of free aortic regurgitation. *Circulation.* 42: 773.
22. Bristow, J. D., R. L. Crislip, C. Farrehi, W. E. Harris, R. P. Lewis, D. W. Sutherland, and H. E. Griswold. 1964. Left ventricular volume measurements in man by thermodilution. *J. Clin. Invest.* 43: 1015.
23. Thorpe, C. R., and F. S. Grodins. 1960. Estimation of left ventricular volumes from thermodilution curves. *Fed. Proc.* 19: 117. (Abstr.)
24. Hosie, K. F. 1962. Thermal-dilution technics. *Circ. Res.* 10: 491.
25. Rapaport, E., B. D. Wiegand, and J. D. Bristow. 1962. Estimation of left ventricular residual volume in the dog by a thermodilution method. *Circ. Res.* 11: 803.
26. Stewart, G. N. 1921. The pulmonary circulation time, the quantity of blood in the lungs and the output of the heart. *Amer. J. Physiol.* 58: 20.
27. Kinsman, J. M., J. W. Moore, and W. F. Hamilton. 1929. Studies on the circulation. I. Injection method: physical and mathematical considerations. *Amer. J. Physiol.* 89: 322.
28. Weissler, A. M., R. G. Peeler, and W. H. Roehl, Jr. 1961. Relationships between left ventricular ejection time, stroke volume, and heart rate in normal individuals and patients with cardiovascular disease. *Amer. Heart J.* 62: 367.
29. Whittaker, A. V., J. A. Shaver, S. Gray III, and J. J. Leonard. 1969. Sound-pressure correlates of the aortic ejection sound. An intracardiac study. *Circulation.* 39: 475.
30. Bush, C. A., R. P. Lewis, R. F. Leighton, M. E. Fontana, and A. M. Weissler. 1970. Verification of systolic time intervals and the true isovolumic contraction time from the apexcardiogram by micromanometer catheterization of the left ventricle and aorta. *Circulation.* 42: 3. (Abstr.)
31. Dixon, W. J., and F. J. Massey, Jr. 1969. Introduction to Statistical Analysis. McGraw-Hill Book Company, New York, 3rd edition.
32. Holt, J. P., A. A. Rhode, S. A. Peoples, and H. Kines. 1962. Left ventricular function in mammals of greatly different size. *Circ. Res.* 10: 798.
33. Swan, H. J. C., and W. Beck. 1960. Ventricular non-mixing as a source of error in the estimation of ventricular volume by the indicator-dilution technic. *Circ. Res.* 8: 989.
34. Maseri, A., and Y. Enson. 1968. Mixing in the right ventricle and pulmonary artery in man: evaluation of ventricular volume measurements from indicator wash-out curves. *J. Clin. Invest.* 47: 848.
35. Hugenholz, P. G., H. R. Wagner, and H. Sandler. 1968. The in vivo determination of left ventricular volume. Comparison of the fiberoptic-indicator dilution and the angiocardiographic methods. *Circulation.* 37: 489.
36. Carleton, R. A., A. F. Bowyer, and J. S. Graettinger. 1966. Overestimation of left ventricular volume by the indicator dilution technique. *Circ. Res.* 18: 248.
37. Burch, G. E., C. T. Ray, and J. A. Cronvich. 1952. Certain mechanical peculiarities of the human cardiac pump in normal and diseased states. *Circulation.* 5: 504.
38. Hefner, L. L., L. T. Sheffield, G. C. Cobbs, and W. Klip. 1962. Relation between mural force and pressure in the left ventricle of the dog. *Circ. Res.* 11: 654.
39. Gault, J. H., J. Ross, and E. Braunwald. 1968. Contractile state of the left ventricle in man. Instantaneous tension-velocity-length relations in patients with and without disease of the left ventricular myocardium. *Circ. Res.* 22: 451.
40. Stead, E. A., Jr., J. V. Warren, A. J. Merrill, and E. S. Brannon. 1945. The cardiac output in male subjects as measured by the technique of right atrial catheterization. Normal values with observations on the effect of anxiety and tilting. *J. Clin. Invest.* 24: 326.
41. Warren, J. V., A. M. Weissler, and J. J. Leonard. 1957. Observations on the determinants of cardiac output. *Trans. Ass. Amer. Physicians Philadelphia.* 70: 268.
42. Bevegard, S., A. Holmgren, and B. Jonsson. 1960. The effect of body position on the circulation at rest and during exercise, with special reference to the influence on the stroke volume. *Acta Physiol. Scand.* 49: 279.
43. Wang, Y., R. J. Marshall, and J. T. Shepherd. 1960. The effect of changes in posture and of graded exercise on stroke volume in man. *J. Clin. Invest.* 39: 1051.
44. Chapman, C. B., J. N. Fisher, and B. J. Sproule. 1960. Behavior of stroke volume at rest and during exercise in human beings. *J. Clin. Invest.* 39: 1208.
45. McGregor, M., W. Adam, and P. Sekelj. 1961. Influence of posture on cardiac output and minute ventilation during exercise. *Circ. Res.* 9: 1089.
46. Reeves, J. T., R. F. Grover, S. G. Blount, Jr., and G. F. Filley. 1961. Cardiac output response to standing and treadmill walking. *J. Appl. Physiol.* 16: 283.
47. Naimark, A., and K. Wasserman. 1962. The effect of posture on pulmonary capillary blood flow in man. *J. Clin. Invest.* 41: 949.

48. Ueda, H., T. Koide, I. Ito, H. Yamada, K. Matsuyama, and M. Lizuka. 1964. Postural changes in blood distribution and its relation to the change in cardiac output. *Jap. Heart J.* 5: 115.
49. Larsson, H., and S. R. Kjellberg. 1948. Roentgenological heart volume determination with special regard to pulse rate and the position of the body. *Acta Radiol. Stockholm.* 29: 159.
50. Linderholm, H., and T. Strandell. 1958. Heart volume in the prone and erect positions in certain heart cases. *Acta Med. Scand.* 162: 247.
51. Ekelung, L.-G., A. Holmgren, and C. O. Ovenfors. 1967. Heart volume during prolonged exercise in the supine and sitting position. *Acta. Physiol. Scand.* 70: 88.
52. Rapaport, E., M. Wong, E. E. Escobar, and G. Martinez. 1966. The effect of upright posture on right ventricular volumes in patients with and without heart failure. *Amer. Heart J.* 71: 146.
53. Weissler, A. M., J. J. Leonard, and J. V. Warren. 1959. The hemodynamic effects of isoproterenol in man. *J. Lab. Clin. Med.* 53: 921.
54. Harrison, D. C., G. Glick, A. Goldblatt, and E. Braunwald. 1964. Studies on cardiac dimensions in intact, unanesthetized man. IV. Effects of isoproterenol and methoxamine. *Circulation.* 29: 186.
55. Paley, H. W., J. Blumenthal, G. Modin, A. D. Levine, and A. J. Noble. 1968. Contribution of left atrial contraction to left ventricular volume in the control state and in response to isoproterenol in man. *Circulation.* 38: 6. (Abstr.)
56. Rushmer, R. F. 1961. *Cardiovascular Dynamics.* W. B. Saunders Company, Philadelphia. 2nd edition. 69.
57. Imperial, E. S., M. N. Levy, and H. Zieske. 1961. Outflow resistance as an independent determinant of cardiac performance. *Circ. Res.* 9: 1148.
58. Wilcken, D. E. L., A. A. Charlier, J. I. E. Hoffman, and A. Guz. 1964. Effects of alterations in aortic impedance on the performance of the ventricles. *Circ. Res.* 14: 283.
59. Dodge, H. T., and W. A. Baxley. 1969. Left ventricular volume and mass and their significance in heart disease. *Amer. J. Cardiol.* 23: 528.
60. Miller, G. A. H., J. W. Kirklin, and H. J. C. Swan. 1965. Myocardial function and left ventricular volumes in acquired valvular insufficiency. *Circulation.* 31: 374.
61. Sonnenblick, E. H. 1968. Correlation of myocardial ultrastructure and function. *Circulation.* 38: 29.
62. Wong, M., E. E. Escobar, G. Martinez, and E. Rapaport. 1965. Effect of coronary artery embolization on ventricular volumes. *Circ. Res.* 16: 518.
63. Bunnell, I. L., C. Grant, and D. G. Greene. 1965. Left ventricular function derived from the pressure-volume diagram. *Amer. J. Med.* 39: 881.
64. Bartle, S. H., and M. E. Sanmarco. 1966. Comparison of angiocardiographic and thermal washout technics for left ventricular volume measurement. *Amer. J. Cardiol.* 18: 235.
65. Garrard, C. L., Jr., A. M. Weissler, and H. T. Dodge. 1970. The relationship of alterations in systolic time intervals to ejection fraction in patients with cardiac disease. *Circulation.* 42: 455.
66. Shaver, J. A., F. W. Kroetz, J. J. Leonard, and H. W. Paley. 1968. The effect of steady-state increases in systemic arterial pressure on the duration of left ventricular ejection time. *J. Clin. Invest.* 47: 217.
67. Blinks, J. R., and J. Koch-Weser. 1961. Analysis of the effects of changes in rate and rhythm upon myocardial contractility. *J. Pharmacol. Exp. Ther.* 134: 373.
68. Mitchell, J. H., A. G. Wallace, and N. S. Skinner, Jr. 1963. Intrinsic effects of heart rate on left ventricular performance. *Amer. J. Physiol.* 205: 41.
69. Sonnenblick, E. H., A. G. Morrow, and J. F. Williams, Jr. 1966. Effects of heart rate on the dynamics of force development in the intact human ventricle. *Circulation.* 33: 945.
70. Sonnenblick, E. H., E. Braunwald, J. F. Williams, Jr., and G. Glick. 1965. Effects of exercise on myocardial force-velocity relations in intact unanesthetized man: relative roles of changes in heart rate, sympathetic activity and ventricular dimensions. *J. Clin. Invest.* 44: 2051.
71. Sarnoff, S. J., and E. Berglund. 1954. Ventricular function. I. Starling's law of the heart studied by means of simultaneous right and left ventricular function curves in the dog. *Circulation.* 9: 706.
72. Sarnoff, S. J. 1955. Myocardial contractility as described by ventricular function curves; observations on Starling's law of the heart. *Physiol. Rev.* 35: 107.
73. Braunwald, E., S. J. Sarnoff, and W. N. Stainsby. 1958. Determinants of duration and mean rate of ventricular ejection. *Circ. Res.* 6: 319.