The Effect of Steady-State Increases in Systemic Arterial Pressure on the Duration of Left Ventricular Ejection Time

JAMES A. SHAVER, FRANK W. KROETZ, JAMES J. LEONARD, and H. W. PALEY

From the University of Pittsburgh School of Medicine, Department of Medicine, Pittsburgh, Pennsylvania

ABSTRACT The effect of steady-state increases in systemic arterial pressure on the duration of left ventricular ejection time was studied in 11 normal male subjects. Methoxamine, a pressor amine of predominantly vasoconstrictor activity but lacking significant inotropic effect, was administered intravenously resulting in an average increase in mean arterial pressure of 27 mm Hg. Heart rate was held constant by high right atrial pacing, and there was no significant change in cardiac output. During methoxamine infusion, when stroke volume, heart rate, and inotropic state were held constant, left ventricular ejection time increased as mean arterial pressure increased. There was a highly significant correlation between the increase in mean systolic blood pressure and the prolongation of left ventricular ejection time ($r = 0.870$). In one subject, an increase in mean systolic pressure of 75 mm Hg prolonged left ventricular ejection time 55 msec, producing paradoxical splitting of the second heart sound. The prolongation of left ventricular ejection time during infusion was not blocked by the prior intravenous administration of atropine sulfate or propranolol hydrochloride, thus ruling out both vagal inhibition of the left ventricle and reflex withdrawal of sympathetic tone as its cause. In three subjects, left ventricular end diastolic pressure was measured and found to be significantly increased. This finding suggests that the normal left ventricle maintains a constant stroke volume in the presence of an increased pressure load by the Frank Starling mechanism. This study concludes that arterial pressure must be included as a prime determinant of left ventricular ejection time along with stroke volume, heart rate, and inotropic state in intact man.

INTRODUCTION

The effect of stroke volume, heart rate, and inotropic state on the duration of left ventricular ejection time has been extensively studied in both man and animals and the results by various investigators are consistent (1–6). However, the effect of increasing systemic arterial pressure has been variably reported to increase, decrease, or have no significant effect on left ventricular ejection time. In the metabolically supported, isolated heart preparation of Braunwald, Sarnoff, and Stainsby (4), substantial changes in mean arterial pressures had little influence on the duration of left ventricular ejection time in six of seven hearts. However, Wallace, Mitchell, Skinner, and Sarnoff (5), in a right heart by-pass preparation, showed that as mean blood pressure was increased left ventricular ejection time decreased, isometric contraction time increased, and the total duration of systole remained unchanged. Weissler, Peeler, and Roehl have reported that when compared to normal controls, no significant difference was found in left ventricular ejection time in a group

A partial report of this work appeared in abstract form. 1966. *J. Clin. Res.* **14**: 261.

Dr. Paley's present adress is the Mt. Zion Hospital, San Francisco, Calif.

Received for publication 23 September 1966 and in revised form 1 September 1967.

of 11 patients with severe hypertension (6). Nevertheless, hypertensive cardiovascular disease has been cited as a cause of paradoxical splitting of the second heart sound (7–9) which presumably is due to prolongation of left ventricular ejection time.

The purpose of this investigation was to study the effect of steady-state increases in systemic arterial pressure on the duration of left ventricular ejection time in the intact human left ventricle. The technique of high right atrial pacing was used to maintain a constant heart rate. By preventing the reflex bradycardia associated with an acute increase in arterial pressure, cardiac output was maintained; and, therefore, stroke volume was held constant. It was possible, then, to study the effect of arterial pressure alone on the duration of left ventricular ejection time when heart rate, stroke volume, and inotropic state were held constant.

METHODS

12 studies were performed on 8 healthy male volunteers and 3 male subjects with functional murmurs, whose ages ranged from 15 to 29 yr. No premedication was administered and all studies were performed in the supine position. A No. 8, bipolar, Zucker[1] catheter was placed at the superior vena cava–right atrial junction. Right atrial pressure was monitored through this catheter while heart rate was held constant by pacing. Arterial pressure was recorded through a 15 cm polyethylene catheter (PE No. 160, 0.045 inch I.D.) that was introduced percutaneously into the left brachial artery. In three subjects, left ventricular pressure was recorded through a radiopaque, polyethylene catheter (PE No. 160) placed retrograde through the right femoral or brachial artery. Cardiac output was determined by the indicator dilution technique. Indocyanine green dye (1.5 mg) was injected through a 90 cm polyethylene catheter (PE No. 50, 0.023 inch I.D.) that had been introduced percutaneously through an antecubital vein into the superior vena cava. Blood was sampled from the brachial artery catheter and delivered to a cuvette densitometer[2] by means of a constant rate, motor driven syringe. Cardiac outputs were performed in duplicate and recorded as the average of the two determinations in all but two observations. Individual determinations checked within $5 \pm 3.7\%$ of their paired average. Calculations were performed after the inscribed dilution curves had been replotted on semilogarithmic paper utilizing the formula of Hamilton, Moore, Kinsman, and Speerling (10).

In each subject, simultaneous recordings of pressures (right atrial, brachial artery, and left ventricular), electrocardiogram, phonocardiogram, and the indirect carotid pulse were made on a multichannel, photographic recording unit[3] at a paper speed of 100 mm/sec, with time markers indicating 0.02 sec (Fig. 1). All pressure measurements were made with P23G Statham pressure transducers.[4] The zero level for pressure was taken as 5 cm below the angle of the sternum with the subject in the supine position. Mean systolic pressure was obtained by planimetry of the systolic portion of five consecutive brachial artery pressure curves. The standard lead II of the electrocardiogram was selected. Heart sounds at the base were recorded with a contact microphone,[5] and care was taken to maintain a constant position on the chest wall at a point where clear inscription of both heart sounds could be made. The indirect carotid pulse was obtained with a standard, funnel-shaped pick-up connected to a P23D transducer. The pick-up was placed over the point of maximal pulsation of the carotid artery, and left ventricular ejection time was measured as the interval from the beginning of the upstroke to the trough of the incisural notch. The QA_2 interval was measured from the onset of the Q wave on the electrocardiogram to the first major vibration of the second heart sound. Each determination of left ventricular ejection time, QA_2 interval, and RR interval was determined from the average of 10 well-inscribed complexes taken in close succession. Heart rate was calculated dividing 60 by the average RR interval. The difference between measured and derived data was evaluated by the method of paired means (11).

Care was taken to familiarize all subjects with the experimental design before the procedure. When all catheters were in place the patient rested for 10–15 min, and control measurements were recorded, after which high right atrial pacing was instituted through the bipolar catheter with a battery powered, external pacing unit.[6] Pacing was accomplished at the slowest possible rate at which complete atrial capture occurred. After a minimum of 5 min of atrial pacing, repeat observations were made. Methoxamine [β-hydroxy-β (2,5 dimethoxyphenyl)-isoprophylamine], a pressor amine of predominantly vasoconstrictor activity but lacking significant inotropic effect (12–15), was then administered intravenously (0.3–0.7 mg/min), which resulted in an average increase of 27 mm Hg in mean arterial pressure. When a new steady state was apparently reached, complete observations were again recorded. Pacing was then discontinued, whereas blood pressure was maintained, elevated with methoxamine, and final measurements were then made. In two subjects, after control observations 2 mg of atropine sulfate was given intravenously. The induced sinus tachycardia was then captured by high right atrial pacing, and the study was continued as described. In one additional subject, 15 mg of propranolol hydrochloride[7] was given intravenously after control observations. High

[1] U. S. Catheter and Instrument, Inc. Glens Falls, N. Y.
[2] Gilford Instruments Laboratory, Oberlin, Ohio.
[3] Electronics for Medicine, White Plains, N. Y.
[4] Statham Instruments, Inc., Hato Rey, Puerto Rico.
[5] Electronics for Medicine, White Plains, N. Y.
[6] Westinghouse, Baltimore, Md.
[7] Inderal, through courtesy of Dr. A. Sahagian-Edwards, Ayerst Laboratories, New York.

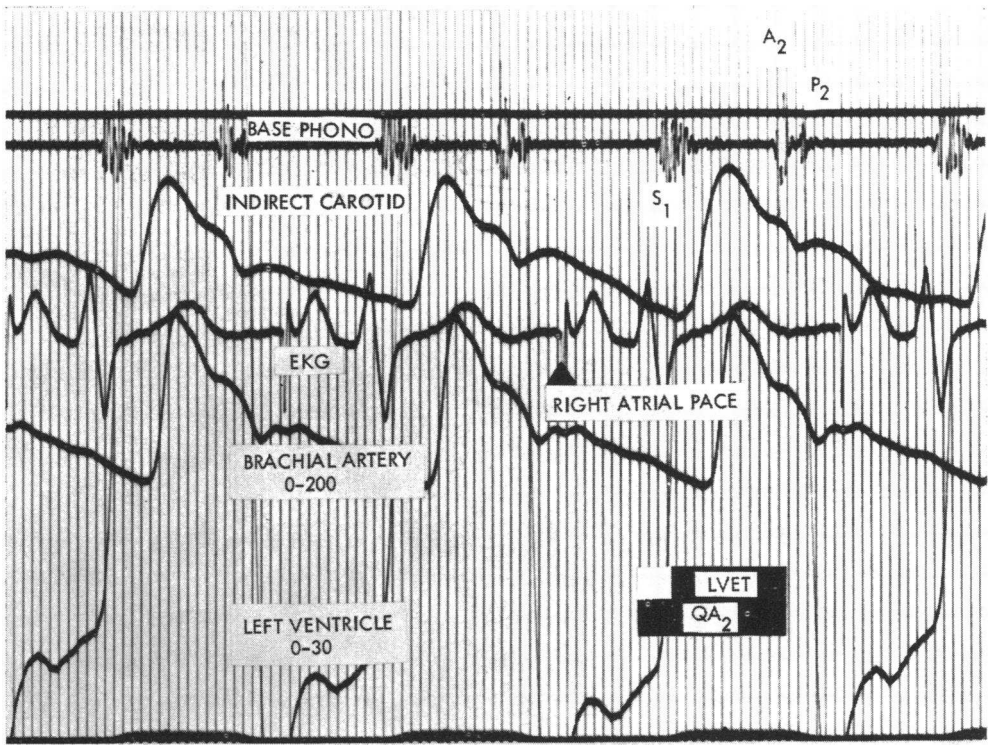

FIGURE 1 Simultaneous recordings of hemodynamic data. From top to bottom: phonocardiogram at the second left interspace; indirect carotid pulse; lead II of the electrocardiogram with high right atrial pace; brachial artery pressure trace: bottom to top line = 200 mm Hg; left ventricular pressure trace: bottom to top line = 30 mm Hg. Left ventricular ejection time (*LVET*) is measured from the beginning of the upstroke of the indirect carotid pulse to the trough of the incisural notch. The QA_2 interval is measured from the onset of the Q wave to the first major vibration of the second heart sound. Paper speed 100 mm/sec; time markers = 0.02 sec.

right atrial pace was established and the above study was repeated.

The following derived calculations were made:

$$\text{Stroke work index (SWI)(g-m/m}^2) = \frac{13.6 \times \text{Sm} \times \text{SVI}}{1000}$$

where

Sm = mean systolic arterial pressure (mm Hg)
SVI = stroke volume index (ml/m²)
13.6 = mercury conversion factor.

$$\text{Total peripheral resistance (TPR)(dyne-sec-cm}^{-5}) = \frac{\text{BA} \times 1.332 \times 60}{\text{CO}}$$

where

BA = mean brachial arterial pressure
1.332 = factor to convert mm Hg to dynes-cm^{-5}
CO = cardiac output (liters/min)
60 = sec/min.

RESULTS

Control vs. control pace. High right atrial pacing was established in the 9 control subjects with an increase in the average heart rate from 68 to 75 beats/min. Pacing produced no significant change in cardiac index ($P > 0.20$). Dependent upon the degree of tachycardia induced necessary to capture the control sinus rhythm, variable effects on stroke volume index, blood pressure, left ventricular ejection time, and other measured parameters were produced and are presented in detail in Table I.

Control pace vs. methoxamine pace. Heart rate was held constant by high right atrial pacing. There was no significant change in cardiac index ($P > 0.20$), and stroke volume index remained unchanged ($P > 0.20$) (Fig. 2). With heart rate and stroke volume index held constant, the infusion of

TABLE I

*Hemodynamic Observations**

Subject BSA Age	Condition	CI	HR	SVI	Arterial pressure				LVET	QA_2	QA_2-ET	RAm	LVED	TPR	SWI
					S	D	Mean	Sm							
		liters/min per m²	*beats/ min*	*ml/min per m²*	*mm Hg*	*mm Hg*	*mm Hg*	*mm Hg*	*msec*	*msec*	*msec*	*mm Hg*	*mm Hg*	*dynes-sec-cm⁻⁵*	*g-m/m²*
E.W.	C	3.18	73	44	119	54	73	90	293	356	63	—	—	917	53
2.00	CP	4.03	86	47	119	65	81	100	271	328	57	—	—	803	64
17	MP	3.86	85	45	167	90	114	123	271	346	75	—	—	1180	76
	M	2.91	61	48	161	81	106	129	287	364	77	—	—	1456	84
T.H.	C	2.93	62	48	119	55	73	103	305	401	96	—	—	829	67
2.40	CP	2.60	65	40	123	63	79	97	309	396	87	—	—	1010	53
20	MP	2.88	65	44	140	81	102	136	329	426	97	—	—	1181	82
	M	2.34	44	53	140	67	95	130	360	441	81	—	—	1353	94
A.P.	C	2.86	60	48	137	67	88	120	298	377	79	7	—	1118	78
2.20	CP	2.94	65	45	135	72	90	119	297	370	73	5	—	1113	72
28	MP 1‡	3.14	65	48	158	88	122	158	320	391	71	7	—	1411	110
	MP 2§	3.14	64	49	230	123	154	194	352	424	74	10	—	1781	112
	M	3.05	53	57	176	88	123	163	355	411	56	10	—	1465	127
M.G.	C	2.92	52	56	134	72	89	113	308	393	85	3	—	1389	86
1.76	CP	3.39	71	47	128	78	98	109	285	362	77	1	—	1312	71
16	MP 1‡	3.28	71	46	150	95	115	135	287	369	82	3	—	1590	85
	MP 2§	3.22	71	45	152	94	115	139	289	374	85	3	—	1621	86
G.B.	C	4.94	78	63	132	68	87	122	303	385	82	1	—	584	105
2.41	CP	5.17	80	65	135	71	87	118	309	383	74	0	—	558	104
24	MP	5.41	80	68	158	87	114	148	321	401	80	1	—	699	136
	M	4.41	70	63	136	69	96	125	329	409	80	1	—	722	107

* BSA, body surface area in m^2; C, control study; CP, study in the control state with rate controlled by pacing; MP, study during methoxamine infusion with rate controlled by pacing; M, study during methoxamine infusion without pacing: A, study after atropine; AP, study after atropine with rate controlled by pacing; A-MP, study after atropine during methoxamine infusion with rate controlled by pacing; A-M, study after atropine during methoxamine infusion without pacing; P, study after propranolol; PP, study after propranolol with rate controlled by pacing; P-MP, study after propranolol during methoxamine infusion with rate controlled by pacing. CI, cardiac index; HR, heart rate; SVI, stroke volume index; S, systolic; D, diastolic; Sm, systolic mean; LVET, left ventricular ejection time; QA_2-ET, QA_2 interval minus left ventricular ejection time; RAm, right atrial mean; LVED, left ventricular end diastolic; TPR, total peripheral resistance; SWI, stroke work index.

‡ MP 1, study during the first level of methoxamine infusion with rate controlled by pacing.

§ MP 2, study following the first level of methoxamine infusion with rate controlled by pacing, with arterial pressure being further elevated by increasing the rate of methoxamine infusion.

‖ CP vs. MP, *P* values performed on 13 paired observations.

¶ CP vs. MP, *P* values performed on 16 paired observations including 13 control paired observations, 2 after atropine, and 1 after propranolol.

TABLE I—(*Continued*)

Subject BSA Age	Condition	CI	HR	SVI	Arterial pressure S	Arterial pressure D	Arterial pressure Mean	Arterial pressure Sm	LVET	QA_2	QA_2-ET	RAm	LVED	TPR	SWI
		liters/min per m²	*beats/ min*	*ml/min per m²*	*mm Hg*	*mm Hg*	*mm Hg*	*mm Hg*	*msec*	*msec*	*msec*	*mm Hg*	*mm Hg*	*dynes-sec-cm⁻⁵*	*g-m/m²*
M.B.	C	5.59	92	61	128	70	94	122	247	312	65	1	7	747	100
1.80	CP	5.06	99	51	133	78	97	119	234	308	74	1	5	851	87
18	MP	5.32	99	54	147	89	116	136	246	328	82	2	8	968	99
	M	4.58	75	61	136	75	101	137	280	357	77	4	14	978	114
R.DP.	C	2.52	51	49	126	73	89	112	334	437	103	7	—	1153	75
2.45	CP	2.95	59	50	127	73	93	115	321	415	94	8	—	1029	78
26	MP 1‡	3.16	59	54	141	80	108	132	332	423	101	7	—	1114	95
	MP 2§	3.24	59	55	157	86	116	136	335	430	95	8	—	1168	102
	M	—	44	—	128	68	99	133	354	441	87	7	—	—	—
R.DR.	C	3.62	78	46	126	66	90	111	279	376	97	2	—	1085	70
1.83	CP	4.10	80	51	122	72	92	111	283	374	91	2	—	979	77
26	MP 1‡	4.15	80	52	134	80	101	124	294	386	92	2	—	1062	87
	MP 2§	3.74	80	47	185	113	141	164	316	398	92	4	—	1647	105
	M	2.46	46	53	161	86	117	—	360	453	93	6	—	2073	—
R.H.	C	3.80	63	60	122	74	93	116	325	—	—	2	8	1124	95
1.74	CP	3.75	70	53	128	75	97	113	312	—	—	0	4	1187	81
29	MP	3.45	70	49	146	88	111	131	332	—	—	2	9	1476	87
	M	2.96	52	57	145	81	104	134	366	—	—	2	10	1614	104
Mean	C	3.61	68	53	127	67	86	112	299	380	84	3	8	994	81
	CP	3.64	73	49	128	72	91	112	293	371	80	3	5	1021	76
	MP	3.74	73	50	159	92	118	143	310	391	86	4	9	1300	97
	M	3.23	56	56	148	77	105	136	336	411	79	5	12	1380	105
P	C vs. CP	>0.20	<0.005	>0.10	>0.40	<0.005	<0.005	>0.50	>0.05	<0.025	<0.050	>0.05	—	<0.025	>0.10
	CP vs. MP‖	>0.20	>0.20	>0.20	<0.001	<0.001	<0.001	<0.001	<0.005	<0.001	<0.010	<0.025	—	<0.001	<0.001
	C vs. M	<0.025	<0.005	<0.05	<0.010	<0.025	<0.005	<0.005	<0.010	<0.025	>0.20	<0.05	—	<0.010	<0.010

TABLE I—(*Continued*)

Subject BSA Age	Condition	CI	HR	SVI	Arterial pressure S	Arterial pressure D	Arterial pressure Mean	Arterial pressure Sm	LVET	QA_2	QA_2-ET	RAm	LVED	TPR	SWI
		liters/min per m²	*beats/ min*	*ml/min per m²*	*mm Hg*	*mm Hg*	*mm Hg*	*mm Hg*	*msec*	*msec*	*msec*	*mm Hg*	*mm Hg*	*dynes-sec-cm⁻⁵*	*g-m/m²*
C.H.	C	2.97	63	47	134	77	93	119	297	402	105	6	—	1262	76
1.98	A	5.74	123	46	157	96	120	136	252	325	73	0	—	844	86
26	AP	6.10	124	49	158	101	117	125	257	325	68	0	—	777	83
	A-MP	5.91	125	48	192	125	158	177	274	339	65	−1	—	1067	116
	A-M	6.20	117	53	190	122	154	167	278	350	72	−2	—	1009	119
A.P.	C	3.82	71	54	133	64	83	104	309	344	35	2	—	775	76
2.24	A	4.43	123	36	133	65	90	108	263	306	43	2	—	726	53
28	AP	4.32	118	37	122	72	87	101	262	316	52	2	—	719	50
	A-MP	4.98	117	43	170	107	132	147	279	331	52	3	—	945	88
	A-M	4.86	111	44	186	118	147	165	297	349	52	3	—	1043	98
R.H.	C	3.87	84	46	131	74	93	110	252	—	—	3	4	1062	69
1.81	P	2.86	71	40	126	75	95	121	271	—	—	4	10	1469	66
15	PP	3.08	71	43	133	81	103	126	272	—	—	5	10	1478	74
	P-MP	3.30	71	45	175	102	130	162	298	—	—	6	15	1737	102
Mean	C	3.59	69	52	128	68	87	112	296	378	81	3	6	1004	79
	CP	3.80	79	48	129	75	94	113	287	364	77	3	6	1015	75
	MP	3.94	79	49	163	96	122	146	305	383	82	4	11	1291	98
	M	3.74	67	54	156	86	114	143	327	397	75	5	12	1301	106
P	CP vs. MP¶	>0.20	>0.20	>0.10	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.025	<0.025	<0.025	<0.001	<0.001

methoxamine produced an average increase in mean arterial pressure of 27 mm Hg, and an average increase in mean systolic pressure of 31 mm Hg. Fig. 3 shows the effect of this increased pressure load on the duration of the various phases of systole. The total duration of systole, as measured by the QA_2 interval, increased significantly ($P < 0.001$). This increase was a result of a significant increase in both left ventricular ejection time ($P < 0.005$) and QA_2-ET interval ($P < 0.010$), the latter being a reflection of isometric contraction time plus ventricular electrical depolarization.

Fig. 4 shows the change in left ventricular ejection time plotted against the change in mean systolic pressure during steady-state methoxamine infusion. Mean systolic pressure was correlated with left ventricular ejection time rather than with mean arterial pressure, as only this phase of the arterial pressure is encountered by the contracting left ventricle. A highly significant correlation coefficient was found between this plot ($r = 0.870$, $P < 0.005$). In one subject, A.P. (Table I), the effect of increased mean systolic pressure on left ventricular ejection time was studied at mean systolic pressure elevations of 39 and 75 mm Hg.

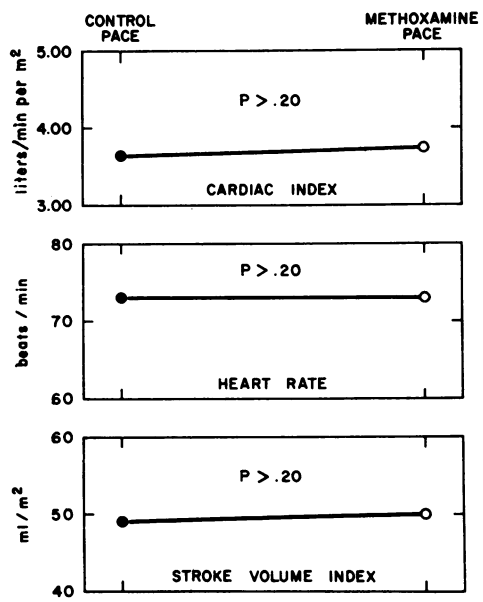

FIGURE 2 Comparison of mean hemodynamic measurements during control pace and methoxamine pace. Cardiac index is unchanged, and with heart rate held constant, there is no significant change in stroke volume index ($P > 0.20$). 13 studies in 9 subjects are included in the mean.

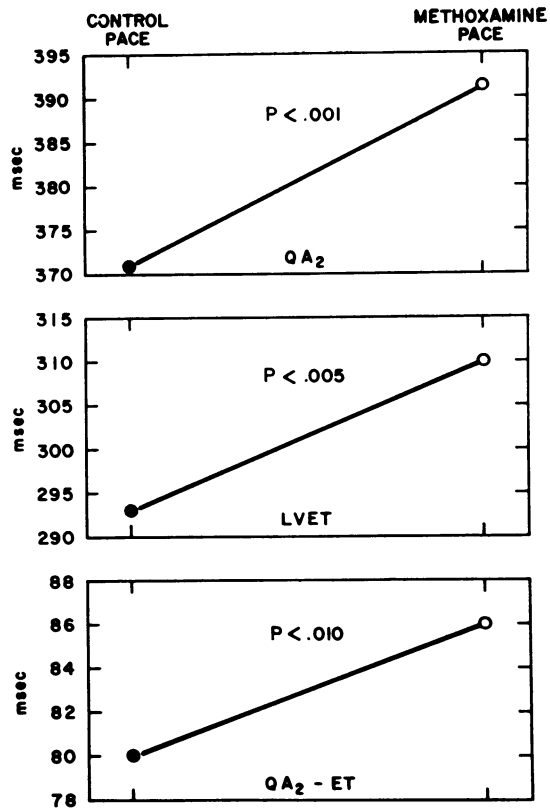

FIGURE 3 Comparison of the mean duration of the phases of systole during control pace and methoxamine pace. During methoxamine infusion, the total duration of systole, as measured by the QA_2 interval, is increased by a significant increase in both left ventricular ejection time (*LVET*) and the electromechanical preejection period (QA_2-ET).

Figs. 5, 6, and 7 show the effect of this elevation on left ventricular ejection time and the splitting of the second heart sound. Fig. 7 shows that with heart rate and stroke volume held constant, an elevation of 75 mm Hg mean systolic pressure prolonged left ventricular ejection time 55 msec, creating paradoxical splitting of the second heart sound.

Venous pressure showed a slight but significant increase ($P < 0.025$) with methoxamine infusion. In two subjects, left ventricular end diastolic pressure was monitored. R.H. increased his left ventricular end diastolic pressure from 4 to 9 mm Hg and M.B. increased his left ventricular end diastolic pressure from 5 to 8 mm Hg, with elevations of mean systolic pressure of 18 and 17 mm Hg, respectively (Table I). Both total peripheral

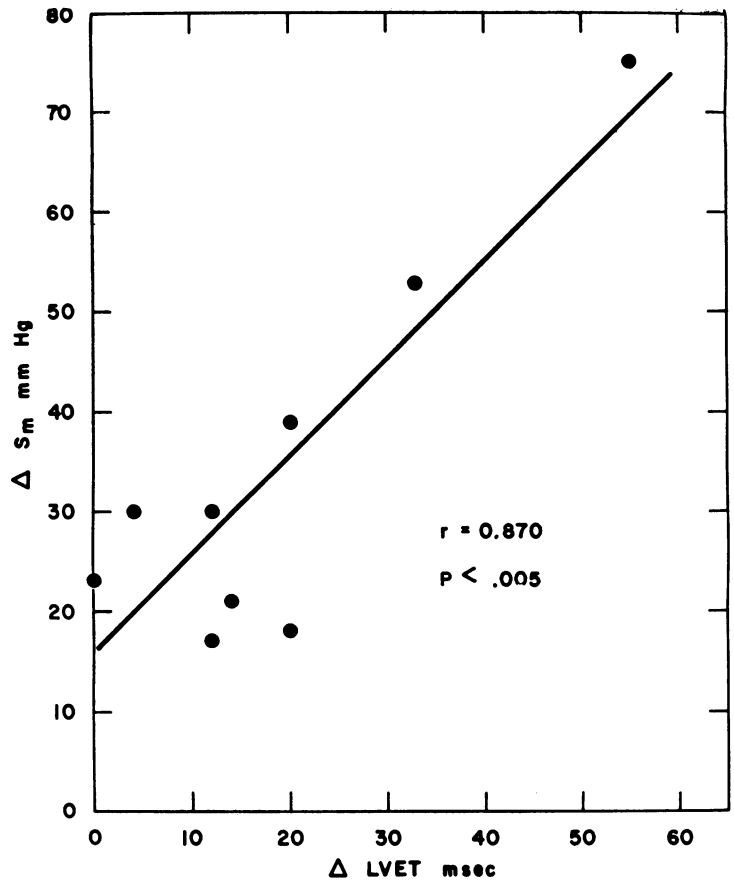

FIGURE 4 Change in mean systolic pressure (*Sm*) plotted against the change in left ventricular ejection time (*LVET*). A highly significant correlation is observed between the two ($r = 0.870$, $P < 0.005$). In subjects A.P., M.G., R.DP., and R.DR., only the maximum response is plotted.

resistance and stroke work index increased proportionately with the blood pressure elevation during methoxamine infusion.

Control vs. methoxamine. Both cardiac index and heart rate were significantly decreased from control values during methoxamine infusion without rate being maintained by pacing. There were significant increases in stroke volume index, blood pressure, left ventricular ejection time, total duration of systole, venous pressure, left ventricular end diastolic pressure, total peripheral vascular resistance, and stroke volume index, which are presented in detail in Table I.

After atropine. The intravenous administration of 2 mg of atropine sulfate caused a significant increase in both cardiac index and heart rate in two subjects, C.H. and A.P. (Table I). In both subjects, when heart rate was held constant by pacing, elevation of the mean systolic pressure with methoxamine caused an increase in left ventricular ejection time, whereas stroke volume index remained unchanged. After cessation of pacing, there was only a slight decrease in heart rate, and cardiac index was unchanged while methoxamine infusion maintained blood pressure.

After propranolol. The intravenous administration of 15 mg of propranolol hydrochloride caused a decrease in both the cardiac index and heart rate (R.H., Table I). When heart rate was held constant by pacing, an elevation of 36 mm Hg in mean systolic pressure by methoxamine caused an increase in left ventricular ejection time of 26 msec and stroke volume index remained unchanged. Left ventricular end diastolic pressure increased from 10 to 15 mm Hg with this increase in mean systolic pressure.

DISCUSSION

By the use of high right atrial pacing, it has been possible to prevent the reflex bradycardia associated with an acute increase in arterial blood pressure (16). With heart rate held constant, the

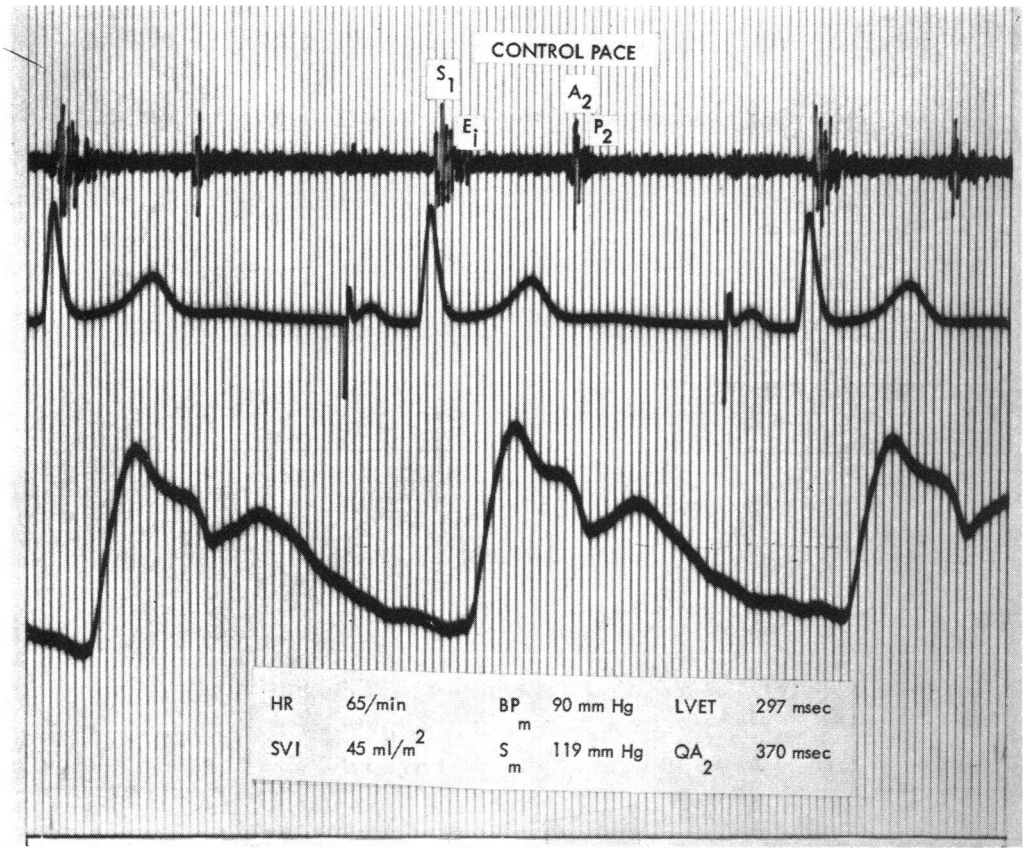

FIGURE 5 Phonocardiogram during control pace (subject A.P.). From top to bottom: phonocardiogram at the second left interspace; lead II of the electrocardiogram with high right atrial pacing; indirect carotid pulse. Note the presence of an early ejection sound and normal splitting of S_2. No diastolic sounds are present. Paper speed 100 mm/sec; time markers = 0.02 sec. Values for left ventricular ejection time and QA_2 interval are the average of 10 well-inscribed complexes.

systemic arterial pressure was increased by the intravenous administration of methoxamine. The assumption was made that during the procedure, neither a positive nor a negative inotropic intervention was imposed upon the subject. It has been well established by previous studies that methoxamine has no significant inotropic effects on the ventricular dynamics in animals (13, 15). Goldberg, Bloodwell, Braunwald, and Morrow (14) have demonstrated that in man the administration of methoxamine does not increase the myocardial contractile force as measured by the strain-gauge arch. Although Brewster, Osgood, Isaacs, and Goldberg (17) have shown evidence of myocardial failure with repeated injections of methoxamine in dogs, this failure was always associated with a highly significant decrease in cardiac indexes, stroke volume indexes, left ventricular stroke work indexes, and systemic arterial pressure. The maintenance of control cardiac output and the increase in both left ventricular stroke work indexes and systemic arterial pressure observed in our subjects after methoxamine infusion are evidence against any significant negative inotropic effect. Also, the maintenance of control cardiac output with pacing and methoxamine, and the subsequent drop in cardiac output with methoxamine alone strongly support the statement by Brewster and coworkers that the cardiac output with methoxamine infusion decreases in proportion to the decrease in heart rate.

During methoxamine infusion when heart rate was held constant by pacing, cardiac index did not change. As a result, stroke volume index remained unchanged, and with the assumption of a constant inotropic state it was possible to evaluate the effect

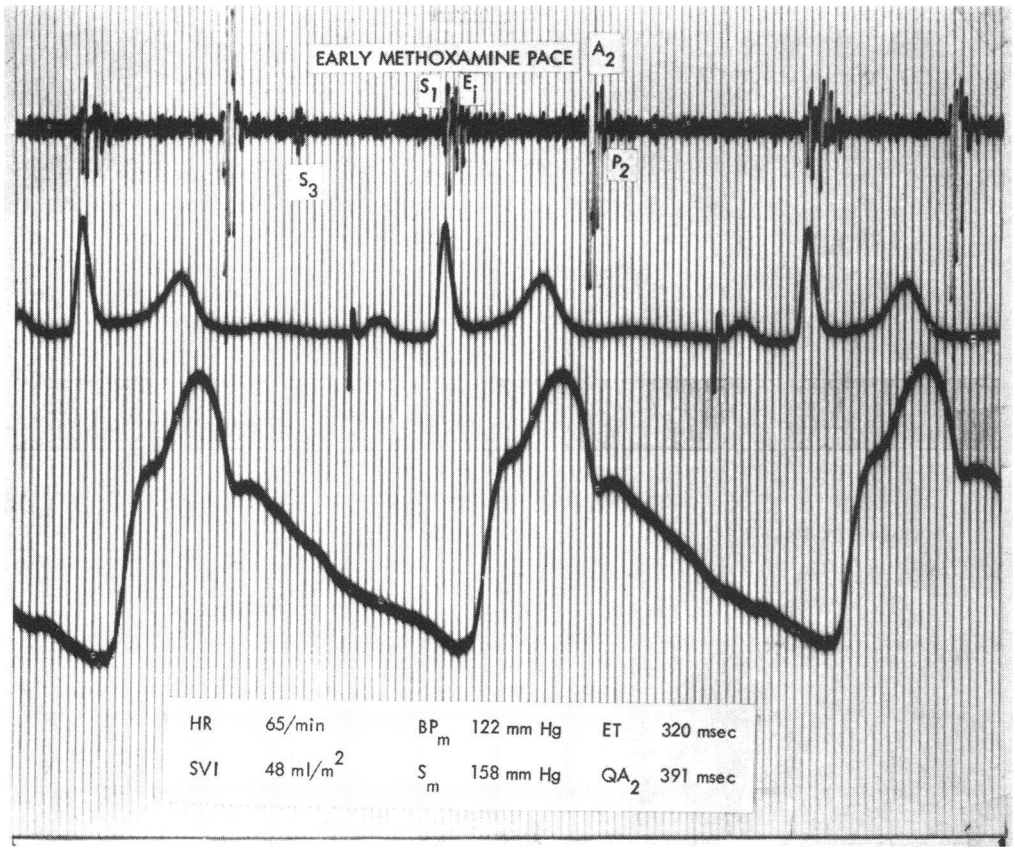

FIGURE 6 Phonocardiogram during early methoxamine pace. With heart rate and stroke volume held constant, methoxamine has increased mean systolic arterial pressure 39 mm Hg. A prominent third heart sound has appeared, and the intensity of A_2 is increased. Left ventricular ejection time has increased 23 msec and splitting has narrowed.

of increased systemic arterial pressure on the dynamics of the intact human left ventricle. As arterial pressure was increased, there was a significant increase in all phases of left ventricular systole. When the prolongation of left ventricular ejection time was compared with the change in the mean arterial systolic pressure, a highly significant correlation was found ($r = 0.870$). Even when there was a marked increase in mean systolic pressure of 75 mm Hg, no significant change was present in stroke volume index. Therefore, the prolongation of left ventricular ejection time of 55 msec, which produced paradoxical splitting of the second heart sound, could not be attributed to left ventricular failure.

In three subjects, in whom left ventricular end diastolic pressure was monitored, there was a marked increase in end diastolic pressure after methoxamine infusion. Braunwald, Frye, and Ross found no alteration of left ventricular end diastolic pressure-end-diastolic-circumference relationship in dogs, when both aortic pressure and cardiac output were varied over wide ranges (18). It is, therefore, probable that the increased end diastolic pressure observed during methoxamine infusion was associated with an increase in end diastolic size. This would be consistent with the findings of Harrison, Glick, Goldblatt, and Braunwald who observed an increase in left ventricular dimensions during methoxamine infusion (19). This increase in left ventricular dimensions was also present after the administration of atropine sulfate and, therefore, could not be attributed to the associated bradycardia. These observations suggest that the normal left ventricle is able to maintain stroke volume in the presence of an increased systemic arterial pressure by increasing the end diastolic fiber length by the Frank Starling mechanism.

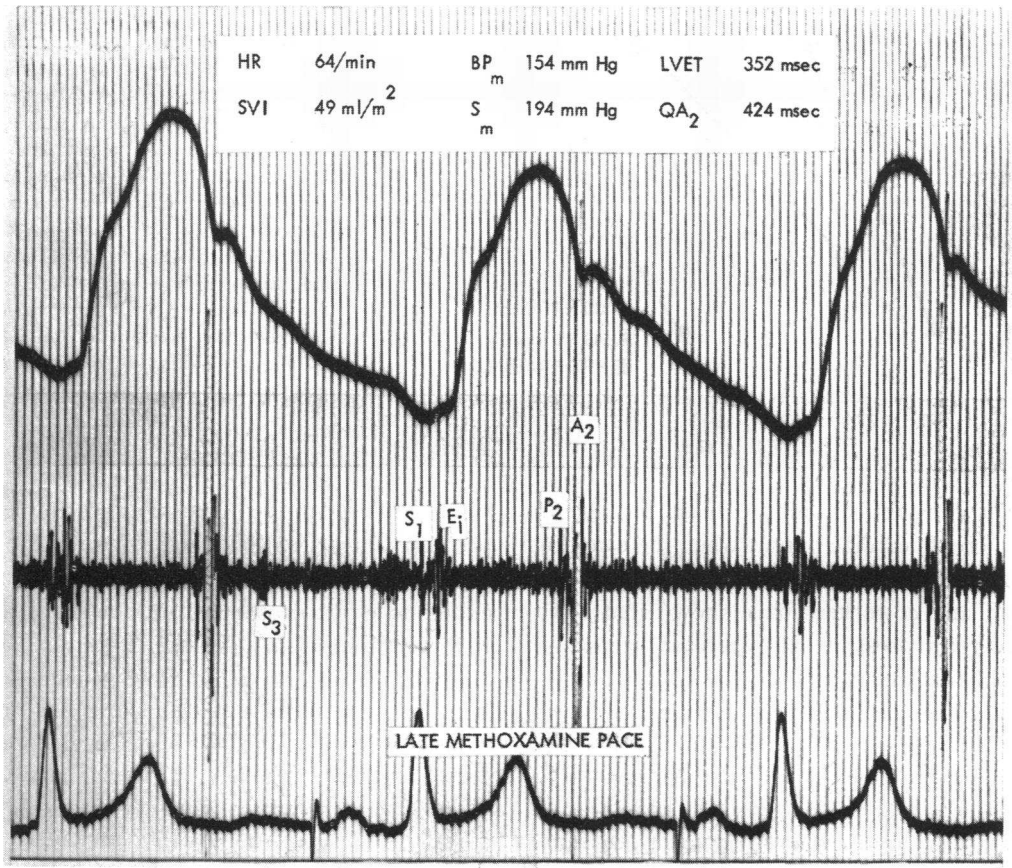

FIGURE 7 Phonocardiogram during late methoxamine pace. An increase in mean systolic arterial pressure of 75 mm Hg has now prolonged left ventricular ejection time 55 msec, producing paradoxical splitting of S_2. There is marked increase in the intensity of A_2, and the prominent S_3 persists. Heart rate and stroke volume index remain unchanged.

Although much controversy exists as to the effect of vagal stimulation on left ventricular contractility, the recent study by DeGeest, Levy, Zieske, and Lipman (20) has indicated a depression of ventricular contractility in both the isovolumetric left ventricle and the pumping left heart. For this reason, two subjects were given 2 mg of intravenous atropine sulfate to completely block the reflex vagal stimulation associated with methoxamine infusion. Results after injection (Fig. 8) were similar in both direction and magnitude to the control subjects, thus ruling out vagal inhibition of the left ventricle as the cause for prolongation of the left ventricular ejection time during methoxamine infusion. It is also interesting to note that when pacing was stopped while methoxamine was continued in the two atropinized subjects, there was only a slight decrease in heart rate, and cardiac output was maintained. This is in sharp contrast to the nine control subjects who developed a significant bradycardia with a consistent decrease in cardiac output when pacing was stopped and methoxamine infusion continued. This, again, is consistent with the observation that the decrease in cardiac output observed with methoxamine infusion is proportionate to the degree of bradycardia. The observation by Wilber and Brust (21) that atropine potentiates norepinephrine, as manifested by increase in both cardiac output and blood pressure, might possibly be explained by the vagal blocking effect of atropine alone. Instead of maintaining only cardiac output, as seen with methoxamine when reflex bradycardia is prevented, norepinephrine, because of its

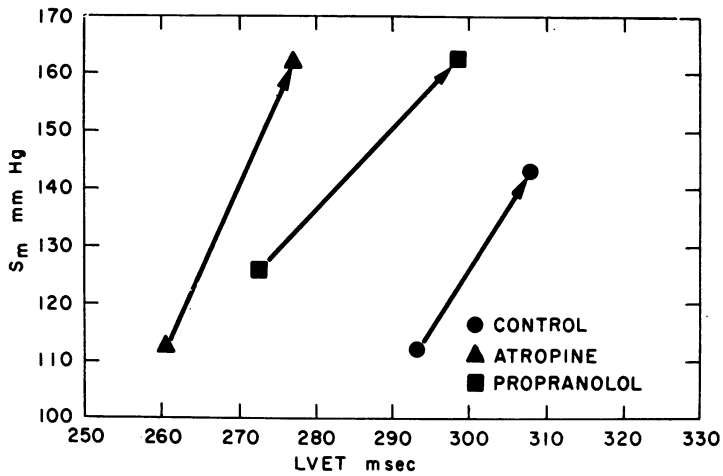

FIGURE 8 Mean systolic pressure (*Sm*) plotted against left ventricular ejection time (*LVET*). Circles represent the mean data of 13 control observations in 9 subjects; triangles, the mean data in the two atropinized subjects; and the squares represent the data after propranolol in a single subject. The direction of the arrow represents the response during the methoxamine infusion, while heart rate and stroke volume were held constant. The response to methoxamine after the administration of both atropine and propranolol is similar in both direction and magnitude to the control response.

potent inotropic effect on the heart, is able to greatly increase cardiac output when the canceling effect of bradycardia is removed.

Sarnoff and coworkers have shown that elevation of carotid pressure can decrease ventricular contractility by reflex withdrawal of sympathetic tone (22). To rule out this mechanism as a possible explanation for the prolongation of left ventricular ejection time during methoxamine infusion, complete beta sympathetic blockade was effected in one subject by the intravenous administration of 15 mg of propranolol hydrochloride. After sympathetic blockade, both left ventricular ejection time and left ventricular end diastolic pressure increased as mean systolic pressure was increased with methoxamine (Table I). Since the mechanism of reflex withdrawal of sympathetic tone could play no part in prolonging left ventricular ejection time after sympathetic blockade, the prolongation of left ventricular ejection time observed in this subject must be attributed to the increased pressure load imposed upon the contracting left ventricle. This response to the methoxamine infusion after propranolol was identical to the response in the control group (Fig. 8). It is, therefore, unlikely that reflex withdrawal of sympathetic tone plays a significant role in the prolongation of left ventricular ejection time in the control group, and that the prolongation consistently observed is due to the increased arterial pressure induced by the methoxamine infusion.

Our findings on the duration of the phases of left ventricular systole are not consistent with the findings of Wallace and coworkers (5). In their right heart by-pass preparation, elevating aortic pressure shortened left ventricular ejection time, prolonged the isometric contraction phase, and had either no effect or showed only a slight decrease in the duration of total systole. They also observed no significant increase in left ventricular end diastolic pressure when aortic pressure was increased as seen in our study. However, in a more recent communication, Mitchell, Wallace, and Skinner (23) have shown that the effect of increasing aortic pressure on both left ventricular ejection time and left ventricular end diastolic pressure was dependent upon the degree of elevation of aortic pressure. With right heart by-pass preparation in the areflexic dog, increasing aortic pressure from 58 ± 2 to 120 ± 4 mm Hg, while stroke volume and heart rate were constant, caused little or no change in left ventricular end diastolic pressure and ejection time. However, a higher elevation of aortic pressure from 114 ± 8 to 139 ± 8 mm Hg caused an increase in left ventricular ejection time and an increase in left ventricular end diastolic pressure. This latter response is identical to our findings. Also, the range of mean aortic pressure and the degree of elevation causing this increase in left ventricular end diastolic pressure and ejection time are similar to the range of mean arterial pressure and degree of elevation in our study.

The findings of Weissler and his coworkers (6) of a normal left ventricular ejection time in a group of 11 patients with severe hypertension is not completely inconsistent with our observations. In fact, if the following sequence of events can be

considered, a possible explanation for the sporadic case of paradoxical splitting of the second heart sound associated with severe hypertensive cardiovascular disease can be made. Since hypertensive cardiovascular disease is usually a slowly progressive process, there is ample time for the ventricle to compensate for the increased pressure load by hypertrophy; and thus, by increasing its mass of contracting tissue, maintain a normal left ventricular ejection time. An analogy can be made between our normal subjects and the compensated patient with hypertensive cardiovascular disease, both of whom have normal left ventricular ejection times. When the normal subject is artificially stressed with an acute rise in arterial pressure, paradoxical splitting of the second heart sound can occur. In the compensated hypertensive, we need only substitute two common clinical situations in the natural history of hypertensive cardiovascular disease and we have created a similar situation. The first of these is a rapid acceleration of hypertension associated with the development of the malignant phase, and the second is the common development of left ventricular failure. The superimposition of either of these acute stresses on the compensated left ventricle, if properly timed and of significant degree, may well explain the rare episodes of paradoxical splitting of the second heart sound seen in hypertensive cardiovascular disease. Moreover, with proper therapy the acute stress can be removed, and the paradoxical splitting will disappear as the ventricle again becomes compensated.

ACKNOWLEDGMENTS

We express gratitude to Mrs. Joanne Spanovich for her interest and nursing assistance, and to Mr. John Fabrizio for his invaluable technical assistance.

This study was supported in part by a grant from the Health Research and Services Foundation (F-10).

REFERENCES

1. Lombard, W. P., and O. M. Cope. 1926. The duration of the systole of the left ventricle of man. *Am. J. Physiol.* **77**: 263.
2. Wiggers, C. J., and L. N. Katz. 1921. The contour of the ventricular volume curves under different conditions. *Am. J. Physiol.* **58**: 439.
3. Remington, J. W., W. F. Hamilton, and R. P. Ahlquist. 1948. Interrelation between the length of systole, stroke volume and left ventricular work in the dog. *Am. J. Physiol.* **154**: 6.
4. Braunwald, E., S. J. Sarnoff, and W. N. Stainsby. 1958. Determinants of duration and mean rate of ventricular ejection. *Circulation Res.* **6**: 319.
5. Wallace, A. G., J. H. Mitchell, N. S. Skinner, and S. J. Sarnoff. 1963. Duration of the phases of left ventricular systole. *Circulation Res.* **12**: 611.
6. 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. *Am. Heart J.* **62**: 367.
7. Gray, I. R. 1956. Paradoxical splitting of the second heart sound. *Brit. Heart J.* **18**: 21.
8. 1966. The Heart, Arteries and Veins. J. W. Hurst and R. B. Logue, editors. McGraw-Hill Book Company, New York. 106.
9. Leonard, J. J., and F. W. Kroetz. 1966. Auscultation, Part IV of Examination of the Heart. American Heart Association.
10. Hamilton, W. F., J. W. Moore, J. M. Kinsman, and R. G. Spurling. 1932. Studies on the Circulation: IV. Further analysis of injection method, and of changes in hemodynamics under physiological and pathological conditions. *Am. J. Physiol.* **99**: 534.
11. Snedecor, G. W. 1956. Statistical Methods Applied to Experiments in Agriculture and Biology. The Iowa State College Press, Ames, Iowa. 5th edition. 49.
12. Aviado, D. M., Jr. 1959. Cardiovascular effects of some commonly used pressor amines. *Anesthesiology.* **20**: 71.
13. Goldberg, L. I., M. DeV. Cotten, T. D. Darby, and E. V. Howell. 1953. Comparative heart contractile force effects of equipressor doses of several sympathomimetic amines. *J. Pharmacol. Exptl. Therap.* **108**: 177.
14. Goldberg, L. I., R. D. Bloodwell, E. Braunwald, and A. G. Morrow. 1960. Direct effects of norepinephrine, epinephrine, and methoxamine on myocardial contractile force in man. *Circulation.* **22**: 1125.
15. West, J. W., S. V. Guzman, and S. Bellet. 1957. Comparative cardiac effects of various sympathomimetic amines. *Circulation Res.* **16**: 950. (Abstr.)
16. Aviado, D. M., Jr., and A. L. Wnuck. 1957. Mechanisms for cardiac slowing by methoxamine. *J. Pharmacol. Exptl. Therap.* **119**: 99.
17. Brewster, W. R., Jr., P. F. Osgood, J. P. Isaacs, and L. I. Goldberg. 1960. Hemodynamic effects of a pressor amine (methoxamine) with predominant vasoconstrictor activity. *Circulation Res.* **8**: 980.
18. Braunwald, E., R. L. Frye, and J. Ross, Jr. 1960. Studies on Starling's Law of the Heart. Determinants of the relationship between left ventricular end-diastolic pressure and circumference. *Circulation Res.* **8**: 1254.
19. Harrision, 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.

20. DeGeest, H., M. N. Levy, H. Zeiske, and R. I. Lipman. 1965. Depression of ventricular contractility by stimulation of the vagus nerves. *Circulation Res.* **17**: 222.
21. Wilber, J. A., and A. A. Brust. 1958. The circulatory and metabolic effects in man of histamine, mecholyl, tetraethylammonium and atropine in the presence of circulating epinephrine and norepinephrine. *J. Clin. Invest.* **37**: 476.
22. Sarnoff, S. J., J. P. Gilmore, S. K. Brockman, J. H. Mitchell, and R. J. Linden. 1960. Regulation of ventricular contraction by the carotid sinus. Its effect on atrial and ventricular dynamics. *Circulation Res.* **8**: 1123.
23. Mitchell, J. H., A. G. Wallace, and S. N. Skinner, Jr. 1966. Relation between end-diastolic pressure and mean rate of ejection of left ventricle. *Am. J. Physiol.* **211**: 83.