An Index of the Contractile State of the Myocardium in Man

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ABSTRACT There is a profound need, on both clinical and physiologic grounds, for a measure of the contractile state of the intact ventricle. Such a measure can be obtained by evaluating the force-velocity relationship with a correction for myocardial fiber length. The force-velocity relation can be expressed as the ratio of maximum rate of pressure rise to maximum isovolumetric pressure, a quantity which was described by Hill as the maximum rate of proportional rise of pressure and which is similar to the velocity constant of a chemical reaction. Division of this ratio by an estimate of ventricular circumference corrects for variations due to differences in initial fiber length.

This index was evaluated in 11 normal subjects and 46 patients with cardiac disease during left heart catheterization. Maximum rate of pressure rise was obtained by electronic differentiation of the ventricular pressure pulse, and ventricular circumference, assuming a spherical ventricle, was calculated from volumes measured by indicator washout.

The contractility index of normal subjects did not differ from that of patients with mitral stenosis, atrial septal defect, or chronic pulmonary disease (patients without left ventricular overloading). In contrast, in patients with left ventricular failure, the indices were more than two standard deviations below the mean value for normal subjects. Such a reduction was not noted in patients with pressure or volume overloading of the left ventricle before the onset of myocardial failure. During exercise, the index rose uniformly in patients without left ventricular disease, responded variably in compensated patients with volume or pressure overloading, and was virtually unchanged in patients with left ventricular decompensation. The administration of isoproterenol or digitalis resulted in increased contractility regardless of the patient's status. It is concluded that the use of this index in physiologic studies of the ventricle and in diagnostic and therapeutic decisions is justified.

INTRODUCTION

In 1938 Hill reported that the reciprocal relationship between force and velocity of contraction was one of the fundamental mechanical properties of skeletal muscle (1). More recently, studies of the isolated papillary muscle have demonstrated that the force-velocity relationship may also be used to characterize the contractile state of heart muscle (2–4). An increase in initial muscle length without an alteration in contractile state has been shown to increase maximum isometric force with no change or with equivalent change in the maximum velocity of contractile element shortening. On the other hand, inotropic interventions were found to increase maximum velocity with smaller

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changes in isometric force. These findings have been confirmed by studies performed on the intact hearts of anesthetized animals (5, 6), the fibers of which are not parallel. In man, Glick, Sonnenblick, and Braunwald (7) have evaluated the force-velocity-length relationship by suturing roentgen-opaque markers to the ventricles during corrective surgery. Weeks later, the motion of these markers was recorded cinefluorographically and intracardiac pressures were measured simultaneously. A constant relationship was found between the velocity of contraction and pressure at a constant length point in each contraction.

An index of the contractile state of the intact ventricle should have many useful applications. It would be of great value in physiologic studies to differentiate the altered dynamics resulting from changes in fiber length (Starling's law of the heart) from those resulting from a change in the contractile state. Such an index would also be of value in identifying patients whose myocardial function is deteriorating before the onset of gross cardiac enlargement or symptoms of heart failure. That surgery performed too late in the course of cardiac deterioration may lead to disappointing surgical results has been confirmed by Rastelli, Kincaid, and Kirklin (8), who reported a significant incidence of persistence of or increase in cardiomegaly resulting from residual impairment of left ventricular performance after replacement of the mitral or aortic valve. Moreover, surgery may be denied to patients despite myocardial failure because of the absence of symptoms. The method of Glick, Sonnenblick, and Braunwald is applicable only after the decision has been made that the heart muscle must be exposed for correction of a mechanical defect. A more easily obtainable index of the contractile state is, therefore, desirable. The purpose of this paper is to describe such an index, based on the force-velocity-length relationship, which may be obtained during routine cardiac catheterization using methods of measurement at present readily available.

METHODS

Study of the force-velocity relation is limited by the circumstance that in cardiac muscle the full value of the amplitude of the active state, corresponding to the tetanic tension and to maximum force in Hill's equation (1), cannot be determined. In addition, maximum velocity obtainable is probably never reached in the intact beating heart due to the onset of isotonic shortening. Since absolute maxima of neither velocity nor force in Hill's equation are achieved in the intact beating heart, substitutions for these quantities were sought. In the intact heart, the maximum rate of pressure rise (MRPR) should be proportional to the maximum rate of contractile element shortening if, in accordance with most theoretical models, the contractile element shortens during isovolumetric contractions while the series elastic element lengthens, and the sum of radii is unchanged. Hartree and Hill (9) suggested that, while the maximum rate of tension rise was useful as a characteristic of the rate of development of the mechanical response to the single twitch of skeletal muscle contracting isometrically, it was necessary to divide the maximum rate of tension rise by the maximum tension to allow for alterations in the mere size of the response. They characterized this quantity as "the maximum rate of proportional rise of tension, a quantity of dimensions minus one in time and similar to the velocity constant of a chemical reaction." They found the maximum rate of proportional rise of tension at a given temperature to be a very constant quantity in frog sartorius muscle. The maximum isovolumetric pressure (MIP) is reached just before the opening of the aortic valve and is a linear function of tension during the isovolumetric period. The maximum rate of proportional rise of pressure is the basis for the contractile index, and should be a linear function of contractile element velocity. Since velocity must be affected by fiber length, the index was normalized for hearts of different size by dividing by the circumferential fiber length, yielding the formula $(MRPR/MIP)/2\pi r$. It was posited that alterations in contractile element performance would be manifested by changes in velocity-force-length ratio and would be evident during the isovolumetric period as changes in the MRPR out of proportion to changes in MIP or fiber length.

The following criteria were established to determine usefulness of the index: (*a*) it should exhibit a relatively narrow range in normal ventricles; (*b*) it should not be significantly depressed in patients with left ventricular disease in the absence of myocardial failure, but be reduced in patients with recent evidence of left ventricular failure, as established by history and physical examination before cardiac catheterization; (*c*) it should be independent of fiber length; and (*d*) it should increase in a predictable fashion with positive inotropic interventions.

46 patients and 11 normal human subjects were studied under mild barbiturate sedation and local procaine analgesia in the steady state. Normal subjects were either volunteers in whom informed consent had been obtained or patients found to be hemodynamically normal at catheterization. The subjects were divided into three groups: group I consisted of subjects with normal left ventricles (11 normal subjects, 9 patients with mitral stenosis, 6 patients with atrial septal defects, and 6 with chronic pulmonary disease). Group II consisted of patients with volume or pressure overloading of the left ventricle (5 patients with predominant and severe aortic

stenosis, 7 patients with predominant and severe aortic regurgitation, and 4 patients with mild aortic valve disease). In each patient with aortic regurgitation, the regurgitant fraction of total aortic valve flow was measured by the upstream sampling method using continuous infusions of indicator. The reliability and accuracy of this method have previously been demonstrated in this laboratory (10, 11). The regurgitant fractions ranged from 50 to 78%, corresponding to moderately severe and severe aortic regurgitation. All patients with volume or pressure overloading of the left ventricle were class I or II and had never been in congestive heart failure except for three patients with mild left ventricular disease whose symptoms were due to severe mitral stenosis. Group III consisted of 9 patients with recent congestive heart failure by history and (or) physical examination. All but one received digitalis and diuretic therapy before catheterization and, on the day of study, were edema free, exhibited no or minimal basilar rales, and were symptomatically improved. All 57 subjects were studied at rest. Satisfactory measurements in a second steady state were accomplished in 33 patients, in 27 during supine exercise on a bicycle ergometer, in 4 during the administration of a continuous intravenous infusion of isoproterenol, and in 2 patients 1–2 hr after intravenous digitalization.

All patients were studied with catheters positioned in the main pulmonary artery, left ventricle, and aortic root. The left ventricle was entered either by the transseptal technic (not used in normal subjects) or by retrograde catheterization of the right brachial artery (6F or 7F NIH catheters, 80 cm long). The catheter tip was located at the apex of the left ventricle in each case. The aortic catheter was either a polyethylene catheter (I.D. 1.13 mm, 70 cm long) introduced percutaneously through a brachial artery by the Stille-Seldinger technic or an NIH catheter introduced by arteriotomy and advanced so that its tip was located just distal to the aortic valve. Pressures were recorded simultaneously from the left ventricle and aorta using Statham strain gauges and an oscilloscopic recorder. Because of its high frequency response, the Statham P23Gb gauge was used in all instances for recording the left ventricular pulse. The first time derivative of the ventricular pulse was obtained using a resistance-capacitance differentiating circuit (time constant 1.1 msec) connected to the output of the left ventricular pressure channel. The maximum error of the differentiator is approximately 0.9% when summing the fundamental with the 10th harmonic. Knopp, Rahimtoola, and Swan (12) have demonstrated that conventional catheter systems and a circuit of this type provide a satisfactory method for recording the derivative within the physiological range of man.

Left ventricular ejection fraction was measured by indicator dilution (13). Indocyanine green dye was introduced into the left ventricle by sudden injection and blood was sampled at rates of 1.25 or 2.0 ml/sec through the aortic catheter and the Gilford densitometer by means of a Harvard withdrawal pump. The sampling dead space ranged from 1.0 to 1.5 ml and the 90% response time for the catheter-densitometer system was approximately 0.6 sec. For these curves, concentration was plotted semilogarithmically as a function of stroke number. Except for the initial one or two beats on some curves, concentrations uniformly fell on a single slope of exponential decay. From this slope the ejection fraction, which is the ratio of stroke volume to end-diastolic volume, was calculated as $1-(C_{N+1}/C_N)$ where C_N is the concentration on any beat, C_{N+1} is the concentration on the succeeding beat, and the concentration ratio (C_{N+1}/C_N) is obtained as the kth root of 0.1, where k is the number of beats required for a one decade fall in concentration. The results of two or more measurements of ejection fraction were averaged in each of the patients for each state.

Cardiac output, except in patients with atrial septal defect, was measured from indocyanine green dilution curves sampled from the aortic root after pulmonary artery or right atrial injection. For these curves, concentration was plotted semilogarithmically as a function of time and extrapolated to 1% of peak concentration. Areas were obtained by summation of the concentrations, and forward flow was calculated by the method of Kinsman, Moore, and Hamilton (14). Mean stroke volume was obtained as the average from two or more such curves in each state. In patients with atrial septal defect, left ventricular stroke volume was obtained from aortic dilution curves during continuous infusions of dye into the left ventricle; the aortic sampling technique has been shown to yield accurate measurements of minute flow (15). End-diastolic volume was calculated as the ratio of mean stroke volume to mean ejection fraction. In the case of aortic regurgitation the appropriate ratio is that of forward stroke volume to ejection fraction, knowledge of regurgitant and total stroke volumes being required only for the calculation of end-systolic and not of end-diastolic volume. It should also be noted that, although mitral regurgitation invalidates measurements of end-diastolic volume by the method employed here, such measurements are valid in aortic regurgitation (16, 17) in which a single exponential slope of decay is recorded (18), because aortic mixing is limited in the presence of turbulent flow resulting in a flat velocity profile (19). The radius of the ventricle was calculated on the assumption that the ventricle was a sphere at the end of the isovolumetric period and the circumferential fiber length was calculated as $2\pi r$.

Representative pressure recording and left ventricular washout curve are illustrated in Fig. 1.

Statistical analysis was performed using conventional methods for small samples. Differences were evaluated by Student's t test. Correlations were measured with the correlation coefficient r.

RESULTS

The results of this study appear in Tables I–III and Figs. 2 and 3.

Patients with normal left ventricles at rest. The contractility index of normal subjects (1.27

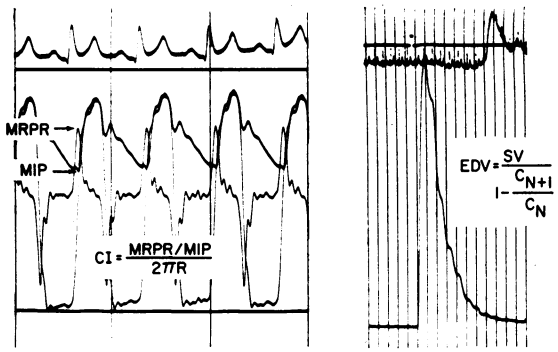

FIGURE 1 Measurement of myocardial contractility. A representative pressure record is on the left and a representative left ventricular indicator washout curve on the right. The maximum rate of pressure rise (MRPR) is indicated as the peak of the first time derivative of the left ventricular pulse. The maximum isovolumetric pressure (MIP) is indicated as the point where aortic and left ventricular pressures are equal just before the opening of the aortic valve. The end-diastolic volume is calculated as the ratio of the stroke volume to the left ventricular ejection fraction, 1- (C_{N+1}/C_N). The contractility index is calculated as the maximum rate of pressure rise (mm Hg/second) per unit of maximum isovolumetric pressure (mm Hg) per centimeter of circumferential fiber length.

$\pm$ 0.13) did not differ significantly from that of patients with mitral stenosis (1.35 $\pm$ 0.16), atrial septal defect (1.34 $\pm$ 0.17), or chronic pulmonary disease (1.41 $\pm$ 0.38). These patients did not differ from normal subjects in heart rate, end-diastolic pressure, MRPR, MIP, or fiber length, despite a diminished cardiac output (Table I). The mean contractility index for all 32 subjects with normal left ventricles was 1.33 $\pm$ 0.21.

Patients with volume or pressure overloading of the left ventricle at rest. The contractility index of patients with severe aortic stenosis (1.83 $\pm$ 0.51) was significantly higher than normal ($P <$ 0.01). This resulted from a more rapid rate of pressure rise, at isovolumetric pressures and fiber lengths insignificantly different ($P < 0.30$) from normal. End-diastolic pressure was significantly greater than normal ($P < 0.01$, Table II). The contractility index was also significantly higher than normal in patients with less severe aortic valve disease (1.76 $\pm$ 0.29, $P < 0.01$, Table II). The mechanism for an augmented contractile response was similar to that seen in severe aortic stenosis. Three of these patients had a marked restriction to cardiac output secondary to severe concomitant mitral stenosis (patients 45, 46, and 48, Table II). This demonstrates the poor validity of cardiac output measurements in evaluating the left ventricular performance of patients with multivalvular disease.

The contractility index of patients with severe compensated aortic regurgitation (1.20 $\pm$ 0.16) did not differ significantly from that of normal subjects ($P < 0.40$). The longer fiber length (24.2 $\pm$ 1.3 cm vs. 19.6 $\pm$ 2.0 cm for normal subjects, $P < 0.01$) was balanced by a lower MIP (58 $\pm$ 10 mm Hg vs 72 $\pm$ 10 mm Hg, $P < 0.01$). Thus, in severe volume overloading, compensated performance is achieved by operating at lower pressures during the isovolumetric period.

Patients with left ventricular failure at rest. The contractility index of this group (0.75 $\pm$ 0.25) was, despite the absence of frank congestive changes at the time of study, significantly lower (Figure 2) than that of the 11 normal subjects, of all subjects without left ventricular overloading, and of all patients with left ventricular overloading (1.54 $\pm$ 0.43, $P < 0.01$). Patients 49 and 57 had predominant and severe aortic stenosis, patients 50, 53, 54, and 56 predominant and severe aortic regurgitation, and patients 51, 52, and 55 alcoholic myocardiopathy (Table III).

Response of the contractility index to inotropic stimulation. 16 patients with normal left ventricles were studied during mild to moderate exercise. In all, the contractility index increased (mean increase 27 $\pm$ 5%, $P < 0.01$). In addition, a high correlation was found between increments in contractility and increments in heart rate ($r =$ 0.76, $P < 0.01$, Fig. 3). This suggests that positive inotropic and chronotropic stimulation during exercise are intimately related under normal circumstances. Of the patients with left ventricular decompensation, three were virtually unchanged while a fourth rose significantly. Patient 49 (Table III) with an aortic valve area of 0.5 cm^2 and a borderline index of contractility at rest, who did manifest an increase, had had an excellent response to digitalization and diuretic therapy. Moreover, exercise did not increase his index to the level found in resting patients with severe compensated aortic stenosis despite an increase in end-diastolic pressure to pulmonary edema levels.

Compensated patients with pressure or volume overloading manifested a variable response to exercise. The contractility index of patients 33 and

TABLE I

Patients with Normal Left Ventricles

Patient	Age, sex	Rest							Exercise						
		HR	CI	MRPR	MIP	EDP	$2\pi r$	Index	HR	CI	MRPR	MIP	EDP	$2\pi r$	Index
Normals															
1	44, M	80	3.90	2194	81	7	21.4	1.27	98	5.42	2714	86	12	22.1	1.43
2	18, M	81	3.64	2545	83	8	22.6	1.37	112	5.08	3911	97	5	22.7	1.78
3	29, F	75	2.70	1377	63	13	19.8	1.10	90	4.42	1909	74	14	20.6	1.25
4	37, M	81	3.14	1575	68	13	20.8	1.11	106	5.45	2382	75	8	21.0	1.51
5	47, F	115	2.43	1191	64	6	16.5	1.13	123	4.54	1461	62	14	19.8	1.19
6	36, F	90	2.53	2031	79	8	15.9	1.47	141	3.35	3230	87	10	17.5	2.
7	16, M	111	4.76	2209	85	6	19.4	1.34							
8	14, M	114	4.46	1800	84	7	18.4	1.17							
9	22, M	63	3.22	2053	70	11	20.6	1.43							
10	43, F	69	3.29	1586	60	12	20.5	1.29							
11	17, F	60	2.96	1580	60	7	19.7	1.34							
Means		85	3.37	1831	72	9	19.6	1.27	112	4.71	2601	80	10	20.6	1.58
Mitral stenosis															
12	54, F	73	3.26	1498	60	9	16.8	1.48	109	4.50	2012	67	7	16.7	1.80
13	40, M	80	2.61	2301	97	12	18.6	1.28	113	5.81	2669	96	11	18.3	1.52
14	32, M	94	4.00	2301	77	7	20.7	1.45	95	7.17	2853	79	11	21.6	1.67
15	26, F	77	2.32	1615	80	12	18.3	1.10	90	2.83	2422	85	11	18.5	1.54
16	59, F	98	2.26	1930	77	11	17.3	1.44	141	2.94	2400	91	13	16.6	1.58
17	32, M	100	2.64	1500	68	6	20.3	1.09	126	3.02	1888	68	4	19.0	1.46
18	45, M	91	2.57	2059	74	6	19.5	1.43							
19	49, F	98	2.38	1815	72	5	18.9	1.34							
20	32, F	82	2.46	2272	80	3	18.5	1.54	124*	4.09	4507	94	3	19.8	2.43
Means		88	2.72	1921	76	8	18.8	1.35	112	4.38	2374	81	10	18.4	1.60
Atrial defect															
21	33, M	80	2.24	1401	62	7	19.0	1.19	143	4.65	3328	85	10	18.9	2.06
22	40, F	101	2.42	1979	79	7	17.4	1.44	120	4.26	2938	94	8	19.8	1.58
23	37, M	96	1.80	1548	68	6	18.1	1.26							
24	13, M	76	3.74	1953	75	11	19.6	1.33							
25	45, F	88	2.11	1206	59	12	17.2	1.19	116*	4.78	3828	49	12	19.6	3.99
26	29, F	88	3.97	1955	62	7	19.5	1.62	116*	6.17	2979	57	5	20.2	2.59
Means		88	2.71	1674	68	8	18.4	1.34	132	4.46	3133	90	9	19.4	1.82
Pulmonary disease															
27	56, M	71	2.55	2421	65	10	20.2	1.84	108	3.81	3724	65	13	20.3	2.82
28	50, M	104	3.26	2150	79	3	19.3	1.41	108	4.16	2552	86	6	20.8	1.44
29	42, M	76	2.19	1779	81	9	20.4	1.09							
30	58, F	70	3.20	2305	59	6	20.4	1.91							
31	44, M	86	3.28	1542	69	9	19.7	1.14							
32	51, M	97	2.63	1771	78	7	21.2	1.07	142*	4.58	2786	70		19.3	1.54
Means		84	2.85	1994	72	7	20.2	1.41	108	3.98	3138	76	10	20.6	2.13

HR, heart rate, beats/min; CI, cardiac index, liter/min per m^2; MRPR, maximum rate of pressure rise, mm Hg/sec; MIP, maximum isovolumetric pressure, mm Hg; EDP, left ventricular end-diastolic pressure, mm Hg; $2\pi r$, left ventricular circumferential fiber length, cm; Index, index of contractility.

* These patients received Isuprel, rather than being exercised. Their data are listed here for convenience only and are not included in exercise means.

34, with severe aortic stenosis, fell more than 20%. Patients 38 and 41, with severe aortic regurgitation, also had a reduced index during exercise and must be considered to have an abnormal response. Patients 39, 40, and 45 (Table II) responded in a normal fashion.

Four patients with normal left ventricles (patients 20, 25, 26, and 32) were given isoproterenol. All had an increase in contractility index. The effect of dose may be seen from the response of patients 20 and 25 (Table I), two women with identical body surface areas, the latter receiving twice the dose of isoproterenol (3 μg/min) as the former. The inotropic response to isoproterenol was not as intimately related to the positive chronotropic response as was the case with exercise.

Patient 37 (Table II) with severe compensated aortic stenosis, and patient 57 (Table III) with severe aortic stenosis and both signs and symptoms of early left ventricular failure, were given 1.5 mg of digoxin intravenously and studied 1 or 2 hr later. Both had an increase in contractility of

TABLE II

Patients with Volume or Pressure Overloading of the Left Ventricle

		Rest							Exercise						
Patient	Age, sex	HR	CI	MRPR	MIP	EDP	$2\pi r$	Index	HR	CI	MRPR	MIP	EDP	$2\pi r$	Index
Severe aortic stenosis															
33	51, M	85	2.67	2534	48	29	19.4	2.73	117	4.05	2649	60	37	20.8	2.12
34	40, F	75	3.31	2066	61	15	21.4	1.58	93	4.05	2316	86	9	21.2	1.27
35	50, M	65	2.41	2838	68	20	24.9	1.68							
36	29, F	68	2.50	1969	48	20	24.3	1.69							
37	45, F	90	2.36	2299	78	20	20.2	1.46	60*	2.14	2300	48	20	21.9	2.19
Means		77	2.65	2341	61	21	22.0	1.83	105	4.05	2482	73	23	21.0	1.70
Severe aortic regurgitation															
38	52, M	60	2.36	1729	47	13	25.9	1.42	85	4.42	1968	62	14	26.8	1.19
39	28, F	92	2.51	1472	50	13	25.4	1.16	118	4.08	2071	55	10	26.0	1.45
40	23, F	94	2.85	1732	52	8	24.9	1.34	143	5.22	2902	72	6	26.4	1.52
41	35, M	61	2.52	1473	54	14	26.1	1.04	86	4.52	1657	81	19	26.4	0.77
42	30, M	72	2.64	1508	66	9	23.0	0.99							
43	22, M	96	3.98	2077	77	21	23.2	1.17							
44	52, F	82	2.54	1653	61	12	20.7	1.31							
Means		80	2.77	1663	58	13	24.2	1.20	108	4.56	2150	68	12	26.4	1.23
Mild aortic valve disease															
45	46, M	98	1.70	2117	64	7	19.5	1.67	144	2.38	2843	64	5	20.7	2.14
46	50, F	63	1.66	2136	82	7	18.7	1.39							
47	54, M	75	3.16	2388	54	15	21.7	2.04							
48	41, F	54	1.23	2236	58	11	20.2	1.92							
Means		72	1.94	2219	64	10	20.0	1.76	144	2.38	2843	64	5	20.7	2.14

All abbreviations are the same as Table I.
* Patient digitalized rather than exercised.

40–50% without a significant change in cardiac output. However, the mechanism of increase was markedly different. Patient 37 developed a lower MIP at the same MRPR while patient 57 had an increase in MRPR with little change in MIP. Whether this difference in response is characteristic of patients with and without failure cannot be determined from the limited data.

Pertinent correlations. Correlations between the contractility index and MRPR, MIP, maximum rate of proportional rise of pressure (MRPR/MIP), and fiber length (end-isovolumetric circumference) were calculated from the data obtained at rest in the 32 subjects with no left ventricular disease and also from the data obtained during exercise in 16 of these subjects. As expected, the index exhibited a significant correlation with MRPR ($r = 0.64$ $P < 0.001$ at rest, and $r = 0.73$ $P < 0.01$ during exercise) but an appreciably better correlation with MRPR/MIP ($r =$

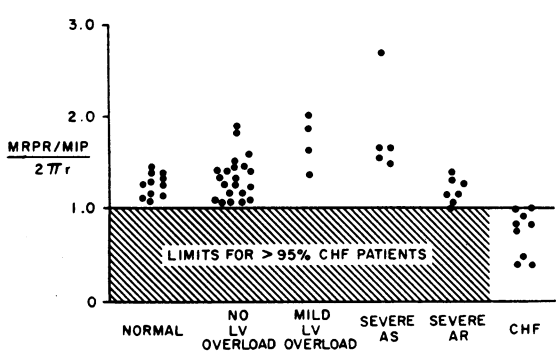

FIGURE 2 The resting contractility index in subjects with and without left ventricular failure. It should be noted that with but one exception the contractility index is beyond the 95% confidence limits for patients with congestive heart failure.

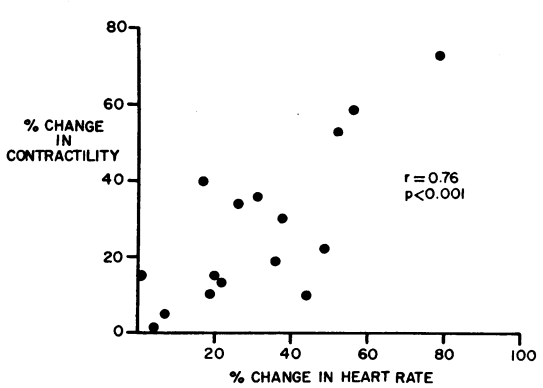

FIGURE 3 The relationship between changes in contractility and changes in heart rate.

TABLE III

Patients with Congestive Heart Failure

		Rest							Exercise						
Patient	Age, sex	HR	CI	MRPR	MIP	EDP	$2\pi r$	Index	HR	CI	MRPR	MIP	EDP	$2\pi r$	Index
49	60, M	58	2.15	1552	70	10	23.2	0.96	89	3.36	2941	86	37	23.7	1.45
50	53, M	62	2.34	1189	57	34	24.4	0.85	77	3.59	1332	67	32	25.0	0.80
51	33, M	86	2.28	854	73	12	23.9	0.49	108	3.40	1110	84	24	24.9	0.53
52	33, M	90	2.43	768	80	15	23.8	0.40	102	3.12	852	82	22	23.0	0.45
53	29, F	76	1.99	1820	101	41	21.8	0.84							
54	56, F	71	1.62	1326	74	16	22.6	0.79							
55	26, M	92	2.45	709	68	33	25.8	0.40							
56	50, M	98	2.46	1531	59	22	25.4	1.02							
57	38, F	98	2.75	1765	76	24	23.2	1.00	96*	2.74	2538	77	16	23.4	1.41
Means		81	2.27	1279	73	23	23.8	0.75	94	3.37	1559	80	29	24.2	0.81

All abbreviations are the same as Table I.

* Patient digitalized rather than exercised.

0.91 $P < 0.001$ at rest, and $r = 0.90$ $P < 0.001$ during exercise). It was independent of fiber length ($r = -0.01$ at rest and -0.16 during exercise) and of maximum isometric pressure ($r = -0.16$ at rest and -0.06 during exercise). The need for normalizing for heart size is evident from the significant relationship ($r = 0.41$ $P < 0.025$) between MRPR/MIP and fiber length at rest. As might be expected, a poorer relationship ($r = 0.26$, not significant) prevailed between these variables during exercise since the latter is known to be associated with significant increase in contractility and inappreciable change in ventricular dimensions in the normal left ventricle.

DISCUSSION

In addition to Hartree and Hill (9), Blinks and Koch-Weser in their recent review (20) have emphasized the importance of evaluating isometric maxima when studying muscle contractility. Fry, Griggs, and Greenfield (21) have stated that the predominant variables defining myocardial contractile performance are tension developed, velocity of contractile element shortening, and muscle length which was found to be more important in the determination of tension-velocity relationship in cardiac muscle than in skeletal muscle. The present study has attempted to evaluate the relationship between the maximum velocity of contractile element shortening and maximum isovolumetric tension with a correction for fiber length. The isovolumetric period was chosen since maximum contractile element shortening is achieved during this time (5, 22) and thereafter declines. The maximum slope of the pressure curve should most closely approximate the maximum slope of the tension curve of papillary muscle contracting isometrically.

An advantage of evaluating events at the end of the isovolumetric phase is that at this moment all radii approach equality. Shortening is confined primarily to the apex-base axis before ejection, and at peak velocity the ventricle most nearly approximates a sphere. Thus, this moment provides an isolength point for evaluating velocity. Moreover, the intensity of the active state, the variability of which is a potential source of difficulty in evaluating contractility, should be near its peak at this point (20). Both instantaneous muscle lengths and the intensity of the active state during ejection are virtually impossible to evaluate without resorting to thoracotomy and the implantation of an electromagnetic flowmeter or roentgen-opaque markers. The foregoing considerations appear to justify the use of the isovolumetric contractility index described in this report.

Siegel and Sonnenblick described an index of myocardial contractility also based on the isometric aspects of myocardial contraction in the intact heart (6). In an innervated, isovolumetric heart in situ, they demonstrated that the ratio of the maximum rate of development of isometric tension (dp/dt) to the integrated isometric tension (IIT), a measure of the total impulse force, was independent of changes in fiber length and remained a constant for any given state of contractility. Cardiac sympathetic nerve stimulation, norepinephrine, calcium, and acetylstrophanthidin altered the mechanics of the isovolumetric ventricle

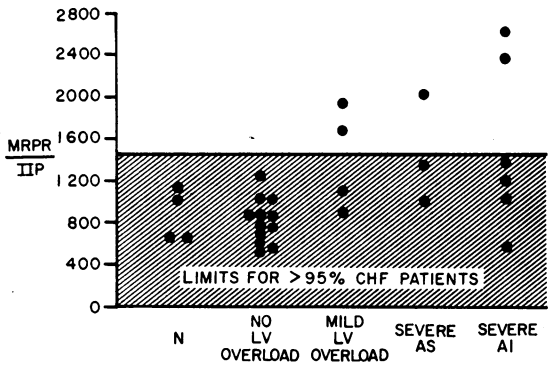

FIGURE 4 The index of Siegel and Sonnenblick in normal and diseased left ventricles.

and produced an increase in their index of contractility. Studies in the closed-chest anesthetized animal and in man (6, 23) demonstrated their index to be sensitive to positive and negative inotropic stimulation and, with use of end-diastolic pressure as an index of end-diastolic fiber length, suggested its independence of fiber length. However, in our study in man, their ratio, expressed as MRPP/IIP (since conversion from pressure to tension requires the same radius term in numerator and denominator), failed to distinguish between the normal and failing left ventricle and was not useful for determination of myocardial compensation in patients with valvular heart disease (Fig. 4). We believe that this problem arises from the absence of a correlation between end-diastolic volume and end-diastolic pressure (13, 17, 24, 25). It is likely that considerable subject-to-subject variation in ventricular compliance exists in both the normal and diseased left ventricle, so that end-diastolic pressure is not a valid index of end-diastolic fiber length. Thus, in the intact beating heart with both isovolumetric and ejection phases, the index of Siegel and Sonnenblick is not conclusively demonstrated to be independent of fiber length. However, granted that their index is theoretically independent of fiber length, the correction for length in our own index is necessary and theoretically sound. The dimensions of the ratio $(dp/dt)/IIT$ are second^{-2} and represent the sum of the times of a series of impulse forces. In contrast, the maximum rate of proportional rise of pressure has the dimensions of second^{-1}, similar to the velocity constant of a chemical reaction, theoretically should not be expected to be independent of fiber length, and has been shown in the present study to be significantly correlated with end-isovolumetric circumference.

It is appreciated that, in the measurements of fiber length employed in this study, several assumptions are implicit: first, that the ventricle approximates a sphere at the end of the isovolumetric phase, second, that its volume can be estimated by dye dilution, and third, that measurement errors are randomly distributed, i.e., that the error of estimate of volume does not differ systematically in ventricles of different size. The necessity for a geometric assumption can, of course, be obviated by substituting end-diastolic volume for end-isovolumetric circumference in the index. In the present series, such substitution does not alter the sensitivity of the index to positive inotropic stimuli, the effectiveness of the index in discriminating between patients with and without evidence of myocardial failure, or the conclusions concerning contractility in patients with ventricular overloading. However, we have chosen to use a fiber length term since a spherical geometry is approximated just before ejection and the conversion of volume to fiber length permits direct comparison of our data with those of numerous other investigators who have employed this assumption in studies of myocardial energetics.

In regard to the measurement of volumes by indicator dilution, we are aware of the criticisms which have been directed against this method. However, in studies previously reported from this laboratory (13), the mean end-diastolic volume in normal subjects at rest was in excellent agreement with measurements obtained in postmortem hearts (26, 27) and with calculations based on previous in vivo measurements of other cardiopulmonary compartments (28, 29). Moreover our results differed insignificantly from those obtained by Folse and Braunwald (16) using radiocardiography and by Miller and Swan (30) using quantitative angiocardiography. Although Kennedy, Baxley, Figley, Dodge, and Blackmon (31), using the method of Dodge, reported a mean end-diastolic volume significantly lower than our own, the actual difference was less than 15% and this was the largest reported difference between our results and those obtained by angiocardiography in normal subjects in a basal state. Larger discrepancies previously reported between angiocardiography and indicator

dilution have, we believe, resulted from comparisons which include low angiocardiographic values obtained with general anesthesia, arrested respiration, and positive intrathoracic pressure (32, 33) and high values obtained by indicator (thermal) dilution in subjects who were not truly normal (17, 24). Using the means, standard deviations, and numbers of subjects reported in studies involving only normal subjects in a basal state, we have previously concluded that the small difference in volumes measured by dye dilution and those measured by angiocardiography may be expressed statistically as follows: the probability is greater than 0.95 that mean end-diastolic volume in a series of normal left ventricles will lie between 74 and 101 ml/m^2 by indicator dilution and between 61 and 91 ml/m^2 by angiocardiography. An even smaller difference was described by Hugenholtz, Wagner, and Sandler (34) who found, in a comparison of the two technics in the same subjects, a difference of only 1%.

Although these considerations, and others cited in our previous report, indicate that dye dilution does provide reliable measurements of end-diastolic volume in the normal left ventricle, it is conceivable that measurements in the larger ventricles are in error. However, in this regard, it should be noted that in aortic regurgitation, in which the largest volumes are reported in all studies, measurements by dye dilution in our laboratory (35, 36) agree very closely with those reported by quantitative angiocardiography (37). Moreover, the mean coefficients of variation in the present series for 37 measurements at rest in nine patients with myocardial failure (5.7%) and for 62 measurements at rest in 16 patients with compensated ventricular overloading (4.8%) differ inappreciably from the mean coefficient of variation (5.1%) previously reported for 146 measurements in 34 normal ventricles, indicating that the error of estimate in ventricles of different size is randomly distributed.

If the "ends" of the muscle are fixed as in an isometric or isovolumetric contraction, the rate of force development by the muscle depends not only on the force-velocity relation of the contractile element, but also upon the stress-strain characteristics of the series elastic. However, the additions of norepinephrine to cat papillary muscle (4), and of norepinephrine or trophandthidin to human papillary muscle (38), do not alter the stress-strain characteristics of the series elastic component. Moreover, the tension-stretch curves of isolated cat papillary muscle are independent of stimulating frequency and of extra-systolic potentiation (2). This suggests that the series elastic component does not participate significantly in physiologic variations affecting contractile matter (2). Thus, acute changes in the index produced by positive and negative inotropic influences should truly reflect changes in contractility, since the maximum rate of proportional rise of pressure should be a linear function of contractile element velocity. One might argue that while it is true that the series elastic is passive and not affected by inotropic interventions, one must consider the possible alteration in stress-strain characteristics produced by the increased preload (initial muscle length) of aortic regurgitation and myocardial failure and by the low aortic diastolic pressure of the former. Parmley and Sonnenblick (39) demonstrated that increasing the preload of normal cat papillary muscle resulted in a stiffer series elastic and a greater MRPR. Alterations in preload should be accounted for in our index by normalization for initial fiber length. Moreover, while series elastic stiffness might have been increased in our patients with myocardial failure or aortic regurgitation, no increase in MRPR occurred. In fact, the tendency was the reverse (Tables II and III). In patients with myocardial failure this most likely resulted from the change in the performance characteristics of the contractile element. In aortic regurgitation, however, it is conceivable that an increased series elastic stiffness from augmented preload is counterbalanced by an increased extensibility due to a lower diastolic pressure so that a given MRPR/MIP reflects a higher contractile element velocity than the same ratio at a higher diastolic pressure. In addition, the maximum isometric pressure (aortic diastolic pressure) may occur in this lesion before the maximum intensity of the active state (generally at 30–40% of maximum isometric pressure) so that the full capacity of the muscle may not be correctly measurable from isometric events. However, the index still clearly discriminates between the presence and absence of myocardial failure in aortic regurgitation and the extent of the performance underestimate, if indeed there is any, cannot be known.

In the light of the above considerations, an underestimate of performance in aortic regurgitation may be responsible for the disparity in contractility index between aortic regurgitation and aortic stenosis. However, it seems just as likely that a higher index in aortic stenosis is related to the increased muscle mass of the left ventricle associated with normal volumes. While individual fibers, such as those of hypertrophied, nonfailing, papillary muscle, might not demonstrate supernormal contractility (40), the chamber as a whole might and probably does operate in this fashon due to the concentric hypertrophy. Patients with aortic stenosis cannot, at normal volumes, compensate for the pressure overloading by a Starling mechanism. They must therefore compensate by an increase in chamber contractility.

That our index of contractility was normal in some patients with severe volume or pressure overloading of the left ventricle is compatible with the natural history of these lesions since patients often have several decades of asymptomatic, normal activity after the recognition of a hemodynamically significant lesion. It is of particular interest that some patients with severe aortic regurgitation and appreciable dilatation of the ventricle performed in a normal fashion since under most circumstances increasing the volume of the heart decreases the mechanical advantage of its myofibrils (41). This would suggest that myocardial failure is prevented in these patients by an increase in the number of myofibrils. Hill pointed out the necessity of avoiding high resting tensions in the study of skeletal muscle since active muscle apparently slips, like a wire strained beyond its elastic limits, if the applied force is too great (1). The slipping is accompanied by an irreversible loss of energy, as heat, which is no longer available for performance of external mechanical work during the contraction. Sonnenblick also observed that the maintenance of high resting tension produced excessive stress relaxation and damage to isolated papillary muscle (3). It would appear that the loss of energy, with stress relaxation, which would otherwise be utilized to achieve normal velocity, may be fundamental to the pathophysiology of heart failure. Overdistention of the ventricle associated with congestive failure results in a contractility index significantly below that of patients with normal left ventricles and patients with left ventricular disease but without myocardial failure. After digitalis and diuretic therapy, the damage of overdistention is reversible to a variable degree as indicated by the wide range of values for the contractility index in the group. It also appears that the index is useful in identifying residual myocardial failure in the absence of frank congestive changes.

Unlike skeletal muscle in which factors other than temperature and fiber length have no appreciable effect on function, heart muscle has the ability to alter its force-velocity relation. Whether the contractility index as defined in this study would identify these changes in state was evaluated during the positive inotropic interventions produced by exercise or the administration of isoproterenol or digitalis. Mild to moderate exercise produced an increase in the contractility index in patients with normal left ventricles. The increase was highly correlated with increments in heart rate. This is compatible with the finding that in the ventricular muscle of most mammals the degree of activation and the rate of tension development in an isometric contraction increase steadily with frequency of stimulation over the entire physiologic range (42). In addition, Sonnenblick, Morrow, and Williams (43) using strain-gauge arches sutured to the right ventricles of patients during cardiac surgery, found a progressive increase in peak velocity of force development without changes in peak force during step-wise increments in heart rate.

While some patients with systolic or diastolic overloading of the left ventricle and a normal resting contractility index responded to exercise in a normal fashion, others had an abnormal response with an unchanged or decreased index. This is best explained by the loss of mechanical advantage which expanding volume produces and with the slipping of fibers under stress and consequent loss of energy, not severe enough to be identified unless additional stress is applied to the ventricle. It is known that the usual force-frequency relationship is abolished if the myocardium is operating near the upper limits of contractile response (43). Moreover, Covell, Chidsey, and Braunwald (44) reported that the response of heart rate and right ventricular contractile force to a stimulation of the sympathetic nervous system was reduced in

dogs with heart failure as compared to the response of control animals.

Four patients with normal left ventricles who were given isoproterenol by continuous intravenous infusion experienced an increase in contractility ranging from 44 to 235%. This is in agreement with the results of Glick, Sonnenblick, and Braunwald (7) who reported a mean velocity increase by the motion of roentgen-opaque markers, and with the report of Sonnenblick, Morrow, and Williams (43) who found a 50% increase in the contractile force of the human right ventricle during anesthesia as measured by strain-gauge arch.

After the administration of digitalis, the contractility index was increased between 40 and 50% without a significant alteration in cardiac output, and despite a 33% fall in heart rate in one of the patients. Sonnenblick, Williams, Glick, Mason, and Braunwald (45) also reported a uniform increase in the contractile state after the administration of this drug. The instantaneous force-velocity relationship as evaluated by roentgen-opaque markers was clearly augmented but the cardiac index either fell slightly or remained unchanged.

We conclude that the contractility index of the ventricle reported in this study is based on firm theoretical grounds and has fulfilled the empirical criteria established for this investigation. The index is a measure of contractility since the maximum rate of proportional rise of pressure is a linear function of contractile element velocity while the effect of varying preload (initial muscle length) on series elastic stiffness and on MRPR should be accounted for by the radius term. The index exhibits a relatively narrow range in normal ventricles, is not depressed in patients with left ventricular disease before the onset of myocardial failure, is significantly depressed in patients with recent evidence of left ventricular failure, increases in a predictable fasion with positive inotropic interventions, and is independent of fiber length. The use of this index in physiologic studies of the ventricle and in diagnostic and therapeutic decisions appears to be justified.

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