The Force-Interval Relationship of the Left Ventricle

PAGE A.W. ANDERSON, M.D., ANDRES MANRING, PH.D., GERALD A. SERWER, M.D., D. WOODROW BENSON, M.D., PH.D., SAM B. EDWARDS, M.D., BRENDA E. ARMSTRONG, M.D., RICHARD J. STERBA, M.D., AND RICHARD D. FLOYD, IV, M.D.

SUMMARY The force-interval relationship — the dependence of cardiac contractility on the rate and pattern of stimulation — has been shown to be independent of preload, but sensitive to the inotropic and disease state of the heart. The force-interval relationship was evaluated for the left ventricles of 42 patients, ages 1.5–20 years, during cardiac catheterization using a micromanometer pressure transducer-tipped catheter and an atrial pacing electrode catheter. The left ventricular (LV) minor axis was monitored echocardiographically, and the end-diastolic dimension (EDD) and posterior wall thickness (PW) were measured. Hearts were paced at a variety of basic cycle intervals, t₀ (1/heart rate), and two test stimuli were introduced at various times during a pause in the regular stimulation (test intervals t₁ and t₂ were measured relative to the last regular systole before the pause). For t₁ < t₀ and t₂ ≥ t₀, P_max of the second test systole was greater than P_max for the last regular systole before the pause (equivalent to postextrasystolic potentiation). The ratio of these values of P_max (test to regular) for systoles with equal LVEDDs, the force-interval ratio, was used to characterize the relationship. Patients were divided into three groups: group 1 (n = 17) patients had normal LVEDD, LVPW and pressure indices. Group 2 (n = 17) patients had increased LVEDD and LVPW but normal pressure indices. Group 3 (n = 4) patients had increased LVEDD and depressed pressure indices. The force-interval relationship was similar for groups 1 and 2: P_max increased monotonically with t₀ or t₁. However, the force-interval ratio was larger for group 2. The relationship for group 3 was different. P_max was a biphasic function of the test interval, increasing for small values of t₁ or t₂ and decreasing for larger values of t₁. The force-interval ratio was smaller than or equal to unity for small values of t₁. This postextrasystolic depression was never found in groups 1 or 2.

THE FORCE-INTERVAL RELATIONSHIP — the contractile response of cardiac muscle to a perturbation in the rate and pattern of stimulation — is exemplified by postextrasystolic potentiation, the response to paired pacing and the staircase that follows a change in rate. The essential properties of the relationship are the same throughout the ascending limb of the length-tension curve.1 The relationship is altered by inotropic interventions (e.g., a change in calcium concentration or exposure to norepinephrine) and by the development of hypertrophy, heart failure and coronary heart disease.2-11 The present study is the consequence of these reports as well as a series of studies from our own laboratory.

Several recent reports have suggested using the force-interval relationship as the basis for an index of cardiac contractility. There are at least four criteria for such an index. The primary criterion is independence of muscle length. Anderson et al.15 found that in the isolated papillary muscle, postextrasystolic potentiation described by the force-interval ratio (F_max of the potentiated contraction divided by F_max of the regular contraction at a given coupling interval and stimulus rate) was constant throughout a wide range of muscle lengths. On the basis of this finding they suggested that the force-interval ratio might be used for such an index. At a constant muscle length, the force-interval ratio changed when the muscle was exposed to ouabain, histamine, norepinephrine, pentobarbital or an altered calcium concentration.13 The new values of the force-interval ratio were also independent of muscle length.13 Thus, the ratio satisfied a second criterion for an index of contractility — sensitivity to the inotropic state of the muscle.

A third criterion for an index of contractility is that the value of the index reflect the condition of the contractile element of the muscle. Preliminary results using light diffraction to measure sarcomere lengths indicate that postextrasystolic potentiation does in fact reflect beat-to-beat changes in the time course of sarcomere shortening14 and that inotropic changes result from changes in the velocity and/or amount of sarcomere shortening.15

A fourth criterion (and perhaps the most important from a clinical point of view) is that the proposed index provides a measurement of the health of the heart. Anderson et al.16 induced right ventricular hypertrophy in cats by banding the pulmonary artery and found the force-interval ratio to be significantly greater than the corresponding ratio for the unbanded cats. Other workers5-11 have also noted changes in the force-interval relationship of patients, as well as animals, that are produced by hypertrophy, heart failure or coronary artery disease.

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From the Duke University Medical Center, Durham, North Carolina.

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Address for reprints: Page A.W. Anderson, M.D., Box 3218, Duke University Medical Center, Durham, North Carolina 27710.

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The same general characteristics of the force-interval relationship hold for the left ventricle of the intact conscious dog. These studies demonstrated that the maximum rate of rise of pressure, $P_{\text{max}}$, was the appropriate quantity to use to form a force-interval ratio for the left ventricle. The strong dependence of $P_{\text{max}}$ on ventricular volume made it necessary to form the ratio from a regular and a potentiated systole that had the same end-diastolic dimension, if the force-interval ratio was to have the following important properties: The ratio did not change when the volume of the ventricle was increased by a saline infusion, and the ratio was sensitive to a change produced by isoproterenol in the inotropic state of the heart.

The present study is a quantitative analysis of the force-interval relationship of the heart in 42 patients. Subjects were divided into three groups: 1) normal heart or no evidence of increased left ventricular size or wall thickness, 2) an increase in left ventricular size or wall thickness without an increase in left ventricular end-diastolic pressure, and 3) an increase in left ventricular size with an increase in left ventricular end-diastolic pressure. We controlled the heart rate and the prematurity of the extrasystole and monitored the ventricular minor axis using echocardiography. We took care to form the force-interval ratio only from systoles that had the same end-diastolic minor axis dimension. This precaution was as important in the present study as in the studies of the intact dog heart cited above. We found that the clinical state, echocardiographic and cardiac catheterization findings of the patient were correlated to the inotropic state of the heart as determined from the force-interval relationship.

![Figure 1](http://circ.ahajournals.org/)

**Figure 1.** Left ventricular pressure recordings (left) and simultaneous echocardiogram (right and lead II of the ECG (bottom trace, left and right). The three systoles, from left, are the last regular systole in the train (basic interval, $t_0 = 450$ msec) and the first and the second test systoles at test intervals $t_1 = 320$ msec and $t_2 = 740$ msec, respectively. $P =$ left ventricular pressure; $\dot{P} =$ first derivative of $P$; $RV =$ right ventricle; $IVS =$ interventricular septum; $LV =$ left ventricle; $PW =$ posterior wall.

**Methods**

**Patients**

Forty-two patients, age 1.5–20 years (mean age 8.6 ± 5.2 years, ±SD) were evaluated during the course of the study. The experimental protocol was approved by the Institutional Clinical Investigation Committee, and we had written permission to carry out each study. All patients were undergoing diagnostic cardiac catheterization at the time of the study.

**Data Acquisition**

Cardiac catheterization was carried out after sedation with meperidine, phenergan and chlorpromazine or diazepam and morphine. The skin was anesthetized with 1% lidocaine. A bipolar pacing catheter was placed in the high right atrium and a Millar PC-355 micromanometer-tipped #5 catheter was placed in the left ventricle. The left ventricular pressure wave form output from a Hewlett-Packard carrier amplifier 8805A was differentiated by a Hewlett-Packard 8814A differentiator, frequency response 0–100 Hz. Electrocardiographic lead II was monitored with a Hewlett-Packard 780-1B. The heart was controlled by atrial pacing at a voltage 10% above threshold with a 5-msec-wide pulse. A programmable stimulator that provided the various rates and patterns of stimulation triggered a Devices isolated stimulator type 2533. The output pulse was passed through a Bioelectric isolater ISB 2.5. The left ventricular pressure wave form, its first derivative, and the ECG were simultaneously recorded on a Mingograf 800 high-speed paper recorder (250 mm/sec) (fig. 1). The entire system had a frequency response that was flat to 100 Hz. The Millar
catheter was statically calibrated at the end of each study in a bath at 37°C. The differentiator was calibrated with a sawtooth wave form.

The left ventricular dimensions along with the ECG were recorded using an Organon Echocardiograph interfaced with a Honeywell strip chart recorder at a paper speed of 50 mm/sec. A 3.5-MHz or, for the smaller patients (< 25 kg), a 4.5 MHz transducer was positioned so as to image the intraventricular septum and posterior left ventricular free wall just below the level of the mitral valve leaflets (fig. 1). The test and regular systoles of a patient were not compared when they had different left ventricular dimensions. In a study on chronically instrumented dogs, the minor-axis dimension was the most sensitive measurement to changes in volume.19 If the volume changed, this dimension changed. Although the echocardiogram may not have measured the true minor-axis dimension, the measured axis was still acceptable, as a change in it would reflect a possible change in left ventricular volume. The patients were separated into groups by using the left ventricular end-diastolic dimension and posterior wall thickness. Those patients who exceeded the ranges of normal (Epstein et al.20 and Henry et al.21) were replaced into groups 2 or 3. Group 3 patients were separated from group 2 on the basis of elevated left ventricular end-diastolic pressure.

**Experimental Protocol**

The pacing protocol adopted in this study was essentially the same one used by Anderson et al.17 to study the force-interval relationship in the chronically instrumented intact awake dog (fig. 2). Our use of $P_{\text{max}}$ to describe this relationship was based on the finding that the force-interval curves were scaled by a change in end-diastolic minor axis (EDD) induced by saline infusion.17

This study was concerned with the changes in contractility that accompany brief perturbations in the pacing pattern (e.g., extrasystolic potentiation). The long-term, slowly equilibrating changes in contractility that follow a sustained change in the pacing rate, e.g., the staircase that follows a change in the stimulus rate, are the subject of a separate study.21 To keep the pacing rate constant throughout an experiment, we used the following pacing protocol:

Trains of stimuli were delivered to the heart. The trains were separated by a pause equal to three basic cycle lengths during which two test stimuli were delivered at variable times, $t_1$ and $t_2$, after the last stimulus in the train. The number of stimuli in each train (N), the interval between the stimuli of the train (the regular or basic interval, $t_0$) and the pause between trains were constant so that the average rate of stimulation was constant during an experiment (although slightly less than during the train). The number of stimuli in each train was made large enough to ensure that the conditions of the heart during each pause, as gauged by $P_{\text{max}}$ and EDD of the last two or three systoles in the train, were the same regardless of the value of $t_1$ and $t_2$ during the previous pause. We found that unless N was made greater than 10, the potentiation produced by the smaller values of $t_1$ and $t_2$
did not completely die away before the next pause. An N value of 15 was found to be satisfactory for every patient in this study.

The shortest basic interval possible for any patient and the shortest interval for which test systoles, s1 or s2, could be elicited were determined by the refractoriness of the atrioventricular conduction system. The longest basic interval used with a given patient was determined by his spontaneous heart rate at the time of the study. The range of spontaneous rates (60-140 beats/min) was large, due to the wide range of ages; usually, the lower the rate, the older the patient. In the studies of two patients with clinical heart failure, the basic heart rate was substantially higher than that of the other patients with similar ages. A comparison of the force-interval relationship for different patients was meaningful only if the basic and test intervals were the same for each patient. Accordingly, each patient was paced at several standard basic intervals; if possible, the patients were paced at a basic cycle interval of 600 msec and 450 msec.

The experiment was divided into two stages. The intervals t1 and t2 were varied systematically during these stages. During the first stage, t1 was changed after each successive train to sample the time course of contractility after the last systole in the train, from the shortest t1 the atrioventricular conduction system would permit up to the value of t2 (inset, fig. 2). The second systole, s2, was placed late in the pause, i.e. t2 was made long. Pmax of the first test systole, s1, was plotted against t1 (fig. 2).

During the second stage, t1 was held fixed. The effect of this fixed extrasystole on the time course of contractility was assessed by changing t2 in each successive train from the shortest t2 that the refractory period of the atrioventricular conduction system would allow to the longest, usually equal to two basic cycle intervals. Pmax of s2 was plotted against t2 (fig. 2). The second stage of the experiment was repeated for several fixed values of t1.

The conduction time from atrium to ventricle usually depended on test intervals t1 and t2. The variations in the delay between atrial stimulation and ventricular depolarization sometimes exceeded 100 msec. In this study, the values of the basic and test intervals used in all the figures and for comparison between patients were measured from the ventricular depolarizations on the ECG.

The experimental procedure was based on the experiments used to analyze the force-interval relationship of the isolated papillary muscle.12 It is convenient here to point out the modifications we have made to adapt these earlier experimental procedures to the study of the force-interval relationship in the intact human heart. The papillary muscle was paced at a low, steady rate. Periodically, extrasystoles (test) were introduced between two regular stimuli, and the contractile responses of the muscle (peak force or its peak derivative) to the extrasystoles were measured. As in the present experiment, the timing of the test stimulus was varied to sample the time course of contractility between contractions at the regular rate (the first stage) and following a premature extrasystole (the second stage). Since the isolated papillary muscle was not spontaneous, it could be paced over a wide range of rates. In particular, it could be paced slowly enough (0.33 Hz) to allow the potentiation after premature depolarizations to fully develop before the next regular contraction.

The intrinsic heart rate of the patients was too fast to allow a wide range of pacing rates. Particularly, if the two test beats were to be introduced during the basic cycle interval, potentiation would not have had time to develop fully and the ventricles would not have had time to fill to a volume equal to that of the previous regular systole before the second test stimulus was applied. Therefore, we paced the patient's heart with a train of stimuli and periodically omitted two regular stimuli to produce a pause. It was during this pause that the two test stimuli were introduced.

Although the isolated papillary muscle can be held isometric (so that the time-dependent changes on contractility are not complicated by the effects of length changes, stress relaxation, or the Anrep effect), in the intact heart, the volume changed continually between systoles so that contractility measured during the pause was determined not only by the time after the previous regular stimulus but also by the volume of the heart. During each experiment t2 was varied so that test systoles could be elicited that have an EDD equal to that of the last regular systole in the train. The effect of heart volume would be the same on Pmax of these test (s2) and regular systoles so that for these systoles, at least, the difference in contractility can reasonably be attributed solely to the perturbation in the rate. The portion of the second-stage curves for which EDD of the test systole equaled that of the last regular systole was termed the isovelocity part of the curve.

The hemodynamic results of the catheterization (Pmax and the end-diastolic pressure at the patient's spontaneous rate) and the echocardiographic results (left ventricular end-diastolic dimension and wall thickness) allowed the patients to be divided into three groups. The results obtained with the analysis of the force-interval relationship were compared for these groups. The force-interval ratios were considered comparable when values of t2 were equal and those of t1 were within 5 msec. The values from these groups were compared with a t test. P < 0.05 was considered significant.

Results

Forty-two patients ranging in age from 1.5-20 years (8.6 ± 5.2 years) were studied. The two-stage force-interval experiment (see Methods and fig. 1) was performed several times on each patient, changing the basic pacing interval (i.e., the basic rate) each time. To make cross-comparisons among patients, standard values of the basic and test intervals were used, although in practice the range of basic and test intervals could not be used for all the patients because of the patient-to-patient variation in intrinsic heart rate and
### Table 1. Patients Undergoing Evaluation of Force-Interval Relationship

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<th>LVPW (cm)</th>
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B) Group 2

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<th>LVPW (cm)</th>
<th>%FS</th>
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<th>Ao (mm Hg)</th>
<th>t&lt;sub&gt;f&lt;/sub&gt; (msec)</th>
<th>t&lt;sub&gt;i&lt;/sub&gt; (msec)</th>
<th>Pmax&lt;sub&gt;te&lt;/sub&gt; (mm Hg)</th>
<th>Pmax&lt;sub&gt;tL&lt;/sub&gt; (mm Hg)</th>
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<td>71</td>
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<td>1800</td>
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<td>600</td>
<td>430</td>
<td>1900</td>
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<tr>
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<td>75</td>
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<td>34</td>
<td>2100</td>
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<td>600</td>
<td>430</td>
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| 23* | 4 | 0.67 | 130 | 4.50 | 0.89 | 43 | 2541 | 104 | 6.0 | 100/36 | 450 | 330 | 2964 | 3379 | 1.14 | TOF, S/P Waterston Shunt, Glenn
| 24† | 4 | 0.59 | 123 | 4.43 | 0.73 | 27 | 1664 | 104 | 5.0 | 92/64 | 450 | 360 | 1456 | 1718 | 1.18 | PA, S/P B-T Shunt, Glenn
| 25* | 4 | 0.65 | 122 | 3.27 | 0.73 | 38 | 2112 | 102 | 1.0 | 102/66 | 450 | 330 | 2508 | 2709 | 1.08 | COA
| 26† | 8 | 1.10 | 81 | 5.18 | 0.67 | 32 | 1157 | 120 | 6.0 | 120/84 | 450 | 330 | 1560 | 2012 | 1.29 | VSD
| 27 | 17 | 1.71 | 73 | 6.22 | 1.00 | 14 | 2164 | 132 | 10.0 | 127/59 | 600 | 475 | 1876 | 2383 | 1.27 | TA, S/P B-T Shunt, Glenn
| 28† | 12 | 1.43 | 71 | 5.00 | 0.75 | 42 | 2934 | 116 | 10.0 | 116/70 | 600 | 430 | 3178 | 4131 | 1.30 | ICH
| 29* | 10 | 1.16 | 103 | 3.70 | 0.90 | 38 | 2990 | 128 | 10.0 | 128/84 | 450 | 330 | 2470 | 3161 | 1.28 | S/P ALCA
| 30† | 6 | 0.78 | 120 | 6.45 | 0.60 | 40 | 1880 | 90 | 10.0 | 100/45 | 450 | 330 | 2115 | 2369 | 1.12 | CV, PS
| 31 | 13 | 1.60 | 75 | 5.39 | 0.84 | 45 | 1827 | 72 | 8.0 | 72/60 | 600 | 495 | 2268 | 2586 | 1.14 | IHSS
| 32† | 9 | 0.98 | 97 | 4.13 | 0.58 | 38 | 1400 | 107 | 5.0 | 107/60 | 450 | 330 | 1653 | 1967 | 1.19 | PAVM
| 33† | 9 | 0.93 | 81 | 3.75 | 0.80 | 42 | 1964 | 138 | 9.0 | 90/64 | 600 | 430 | 2059 | 2627 | 1.28 | AS
| 34† | 8 | 1.03 | 91 | 4.32 | 0.82 | 46 | 2629 | 101 | 7.5 | 100/56 | 450 | 330 | 2919 | 3328 | 1.14 | TA, S/P Bilateral B-T Shunt

Mean 9.5 93.6 38.9 2085 115.1 7.3 109.2
± SD ±19.8 ±8.5 ±498 ±16.5 ±2.7 ±17.9

C) Group 3

| 35 | 20 | 1.67 | 71 | 6.41 | 0.96 | 21 | 900 | 113 | 16.0 | 112/60 | 600 | 410 | 1020 | 989 | 0.97 | TA S/P B-T Shunt
| 36 | 2 | 0.425 | 130 | 3.20 | 0.43 | 25 | 812 | 92 | 20.0 | 92/52 | 400 | 265 | 1008 | 847 | 0.84 | VSD S/P TOF
| 37 | 15 | 1.56 | 77 | 5.87 | 0.78 | 40 | 1080 | 109 | 19.0 | 109/44 | 600 | 410 | 1188 | 1164 | 0.98 | DORV, PS S/P Bilateral B-T

Mean 12.8 102 24 948 106 22.8 105.8
± SD ±7.6 ±32.4 ±12.4 ±117 ±9.5 ±9.0 ±8.3

38‡ 14 1.60 130 6.14 0.53 10 1000 110 36.0 110/70 450 330 1020 1020 1.00 CCM

*Data shown in figure 5B.
†Data shown in figure 5A.
‡Received digoxin within 48 hours before study.
§Received dopamine and nitropressure.

Abbreviations: BSA = body surface area; HR = heart rate; LVEDD = left ventricular end-diastolic dimension; LVPW = left ventricular posterior wall thickness; %FS = percent fractional shortening; Pmax = maximum rate of rise of left ventricular pressure; LVP = left ventricular pressure; LVEDP = left ventricular end-diastolic pressure; Ao = aortic pressure; ts = basic pacing interval; tI = interval between last regular systole and first-stage test systole; Pmax t4 = Pmax of last regular systole; Pmax t5 = Pmax of second-stage test systole; FIR = force-interval ratio; PS = pulmonary stenosis; ASD = atrial septal defect; R/O ASD = normal heart catheterized to rule out ASD; AV = aortic valve; S/P = status post-repair or procedure; TOF = tetralogy of Fallot; VSD = ventricular septal defect; PA = pulmonary atresia; TA = tricuspid atresia; PSM = paradoxical septal motion; AI = aortic insufficiency; TGV = transposition of the great vessels; COA = coarctation of the aorta; B-T = Blalock-Taussig shunt; ALCA = partial ligation anomalous left coronary artery; CV = common ventricle; IHSS = idiopathic hypertrophic subaortic stenosis; PAVM = pulmonary arteriovenous malformation; AS = aortic stenosis; DORV = double outlet right ventricle; CCM = congestive cardiomyopathy; ICH = idiopathic concentric hypertrophy.
refractoriness of the atrioventricular conduction system. For example, several of the older patients had low heart rates and could be paced at 600–800 msec, while most of the very young patients could not be paced at intervals above about 450 msec. On the other hand, the functional refractory period of the atrioventricular conduction system of some of the older patients was greater than 480 msec.

The force-interval relationship was not evaluated in two of the patients who could not be paced properly because of spontaneous supraventricular tachycardia and catheter-induced premature ventricular depolarizations. Another limitation was the spontaneous increase in heart rate that sometimes occurred when the patient — usually the younger patient — became agitated with the introduction of a catheter or the positioning of the echocardiographic transducer on the chest. The data from two patients that increased their intrinsic heart rate by over 50% during the course of the study were not included in this report.

The remaining 38 patients were divided into three groups according to their left ventricular posterior wall thickness and end-diastolic dimensions and end-diastolic pressure measurements.

Group 1 consisted of 17 patients (7.1 ± 5.0 years) who had echocardiographic end-diastolic dimensions and posterior wall thickness that were normal for their body size (table 1A). The pressure indices, the end-diastolic pressure (5.5 ± 2.4 mm Hg) and \( P_{\text{max}} \) (2087 ± 662 mm Hg/sec), were normal.

Group 2 consisted of 17 patients (9.5 ± 4.4 years) who had an increased echocardiographic left ventricular EDD or posterior wall thickness for their body size (table 1B). However, these patients, like the patients from group 1, had normal pressure indices: end-diastolic pressure (7.3 ± 2.7 mm Hg) and \( P_{\text{max}} \) (2085 ± 498 mm Hg/sec).

Group 3 consisted of four patients (ages 2, 14, 15 and 20 years) who had elevated left ventricular end-diastolic pressures (16–34 mm Hg) and depressed \( P_{\text{max}} \) (812–1080 mm Hg/sec). The echocardiographic left ventricular end-diastolic dimensions were abnormally large in all four (table 1C).

**Force-Interval Relationship Results**

The pacing protocol used to evaluate the force-interval relationship was described in the Methods section and in figure 2. \( P_{\text{max}} \) of the test systole was plotted against the test interval \( t_1 \) or \( t_2 \) (the RR interval between the last regular systole in the train and the first or second test systole). The resulting curves, the force-interval curves, were found to be distinctive for each group of patients (see below groups 1, 2 and 3).

The EDD was measured for the last systole in the train and for each test systole. It was found that as \( t_1 \) approached the basic interval (e.g., \( t_0 = 600 \) msec, \( t_1 = 500 \) msec) the EDD of \( s_1 \) approached or equaled that of the last regular systole in the train. For the second stage, we found that the EDD of the test systole generally equaled the EDD of the last regular systole in the train when \( t_2 \) was approximately equal to \( t_1 + t_0 \).

In all the force-interval curves, the test systoles that had the same EDD as the last regular systole in the train were indicated either by solid lines (fig. 2) or by use of filled symbols (figs. 3 and 4). These systoles can be compared without the uncertainty and inconvenience of having to correct for differences in ventricular volume. The force-interval ratio, the ratio of \( P_{\text{max}} \) of these systoles, has been shown to be independent of ventricular volume, making the ratio a useful measurement for comparing one heart to another.

![Figure 3](http://circ.ahajournals.org/)

**Figure 3.** Comparison of second-stage force-interval curves from two patients in group 1. Panels A and B are from an 18-year-old (patient 9); in A, \( t_0 = 450 \) msec and \( t_1 = 340 \) msec; in B, \( t_0 = 600 \) msec and \( t_1 = 380 \) msec. Panel C is from a 4-year-old (patient 12); \( t_0 = 450 \) msec and \( t_1 = 340 \) msec. The different symbols denote whether the end-diastolic dimension of the test systole, \( s_2 \), was smaller than \( s_1 \) (O), equal to (●), or greater than (○) the end-diastolic dimension of the last regular systole in the previous train. In A at the faster rate \( P_{\text{max}} \) rises over the isoleth period, but at the slower rate the isoleth period occurred during the plateau. In C when \( t_2 \) was twice \( t_0 \), \( P_{\text{max}} \) fell below the plateau.
Group 1

The force-interval curves from this control group were similar to those in the conscious dog. Figure 2 shows the results from a first stage of the force-interval experiment. $P_{\text{max}}$ of the test systole was plotted against $t_1$. As $t_1$ was increased from the shortest time (determined by the refractoriness of the atrioventricular conduction system), $P_{\text{max}}$ increased monotonically with the value of the previous regular systole. The curve rose steeply for short test intervals, more slowly for longer intervals.

The force-interval curve for the second stage of the experiment described the way $P_{\text{max}}$ of the test systole, occurring after a premature systole with a fixed $t_1$, depended on $t_2$ (inset, fig. 2). Two examples of second-stage curves are shown in figure 2, $t_1$ of 360 msec for the upper curve and 420 msec for the lower. As with the first stage, $P_{\text{max}}$ increased monotonically with $t_2$. The curve was steepest for short intervals, flat or almost flat for longer intervals; we term the flat portion the plateau of the curve. The plateau values of the second-stage curves were higher than $P_{\text{max}}$ of the last regular systole — the value that the first-stage curve reached (i.e., the force-interval ratio exceeded unity).

For any patient the force-interval ratio depended on $t_0$ (the basic interval, i.e. heart rate) and $t_1$. For a constant $t_1$, the ratio became smaller with decreasing $t_0$ (fig. 5). For a constant $t_0$, the ratio increased as $t_1$ was decreased (except, occasionally, for early values of $t_1$).

Therefore, both basic and test intervals had to be the same if one patient was to be compared to another, or to himself at a different time.

In the older patient, the plateau phase of the second stage curve was most pronounced when the basic interval was long, e.g. 600–800 ms. (fig. 3-B), but could also be seen in the curves of the younger child with shorter basic cycle lengths, i.e. 350–450 msec (fig. 3C).

When an older patient who had a low spontaneous heart rate ($t_0$ of 800–1000 msec) was paced at a much shorter basic interval (450–500 msec), the EDD of the last regular systole in the train was considerably less than at the slow rate. If $t_1$ or $t_2$ was longer than $t_0$, the ventricle continued filling well beyond the EDD of the last regular systole. Consequently, the force-interval curves had an upward slope rather than the usual plateau during the isochronous part (compare the data at two rates from an 18-year-old; filled symbols in 3A when $t_0 = 450$ msec with those in 3B when $t_0 = 600$ msec).

The curve in figure 3C was also obtained at a basic interval of 450 msec as was that in 3A; however, the patient who provided the data in 3C was 4 years old and had a higher intrinsic heart rate. The prolonged plateau portion of the curve in figure 3C coincides with the isochronous part of the curve. The duration of the plateau was 50–100 msec generally when the spontaneous basic interval was within 200 msec of the paced interval. However, the plateau occurred after
the isolument part of the curve in figure 3A (compared with 3C), indicating that contractility increased more slowly in the older than in the younger heart. Since the plateau did not occur during the isolument part of the curve (fig. 3A), we could not be certain whether the true force-interval ratio for these values of \( t_o \) and \( t_i \) was obtained because of the interaction of ventricular filling and heart rate. However, the later data point (note the filled symbol underneath the half-filled symbols) would suggest that it was.

Figure 3B shows the effect of EDD on the second-stage curve and underscores the importance of monitoring the ventricular dimension. The curves had a plateau between 900–1000 msec. Beyond the plateau the rise in \( P_{\text{max}} \) was accompanied by an increase in EDD. The use of these late values would have resulted in an erroneously large ratio.

Figure 3C shows a decline in the plateau of the second-stage force-interval curve at large values of \( t_i \). This was sometimes seen when \( t_i \) equaled or was greater than about twice the basic interval. It was probably not due to a decline in contractility so much as to a decline in aortic diastolic pressure during the long diastole. As Quinones et al.\textsuperscript{22} and others\textsuperscript{10, 11} have pointed out, if the aortic pressure drops below the pressure at which dP/dt of the isovolumic ventricle reaches its maximum value, the opening of the aortic valve will diminish the measured value of \( P_{\text{max}} \). To study this effect, the two-stage experiment was partially repeated for a few patients with the Millar catheter in the aorta. As \( t_i \) was shortened, \( s_i \) became mechanically ineffective. This enhanced the drop in the aortic diastolic pressure at the time of the second test systole, \( s_i \). Conversely, the longer \( t_i \) the more mechanically effective was \( s_i \) and the less the drop in diastolic aortic pressure. For example, in one patient paced at a basic interval of 450 msec and \( t_i \) of 300 msec, the aortic diastolic pressure decreased 15 mm Hg from that of the previous regular systole at a time when the EDD of the test and regular systoles were equal, compared with the 5 mm Hg drop in diastolic aortic pressure when \( t_o \) was 450 msec and \( t_i \) was 350 msec.

The heart rate affected \( P_{\text{max}} \) of the last regular systole in the train. Even though EDD usually fell with an increasing rate, there was a small but significant increase in \( P_{\text{max}} \) with an increase in rate for all the patients (e.g., 600 msec \( P_{\text{max}} \) 2227 ± 957 mm Hg/sec vs 450 msec \( P_{\text{max}} \) 2651 ± 1060 mm Hg/sec, \( p < 0.001 \)). However, the true increase in \( P_{\text{max}} \) resulting from the increase in rate could not be determined due to the associated fall in EDD.

**Group 2**

This group comprised patients with abnormal left ventricular dimensions and normal left ventricular end-diastolic pressures. Qualitatively, the force-interval curves resembled those from patients in group...
During the first stage, \( \dot{P}_{\text{max}} \) of the test systole increased monotonically with \( t_0 \), to a value equal to \( \dot{P}_{\text{max}} \) of the last regular systole in the train. During the second stage of the experiment, \( \dot{P}_{\text{max}} \) increased monotonically with increasing \( t_2 \) to a plateau value greater than \( \dot{P}_{\text{max}} \) of the last systole of the train. The force-interval ratio depended on the basic interval (\( t_0 \)) and on \( t_1 \), as it did for the patients in group 1 (fig. 5). For a given \( t_0 \), the ratio declined with increasing \( t_0 \), and for a given value of \( t_1 \), the ratio declined with a decreasing \( t_0 \) (i.e., an increase in heart rate while the timing of the premature systole was unchanged resulted in a decrease in postextrasystolic potentiation).

There was a quantitative difference between the two-stage experimental results of group 1 and group 2 patients (fig. 6). For given basic and test intervals (e.g., \( t_0 = 600 \text{ msec} \) and \( t_1 = 430 \text{ msec} \)), the mean potentiation was significantly higher (\( p < 0.001 \)) in the patients in group 2 (1.31±0.09) compared with the patients in group 1 (1.15±0.04) (fig. 6A). In this case the groups did not overlap. Essentially the same results were obtained at faster rates — the hearts of group 2 patients potentiated more than the normal ones. At the high rates (e.g., \( t_0 = 450 \text{ msec} \), fig. 6B) the overall potentiation was less for both groups, so the distinction between groups was less striking but still significant (\( p < 0.001 \)). Some of these patients could only be paced at this interval or faster, as they were relatively tachycardic for their age and clinical status (e.g., patient 25 in table 1B, a 4-year-old with aortic stenosis and coarctation of the aorta whose resting heart rate during the study was greater than 120 beats/min, provided the lowest ratio in the group 2 patients in fig. 6B). This increase in rate might have been a reflection of a change in sympathetic tone that would have altered the inotropic state from that of the rest state (see Discussion).

**Group 3**

These four patients, like the patients in Group 2, had abnormal left ventricular dimensions with a large left ventricular EDD. However, unlike the patients in group 2 they had elevated left ventricular end-diastolic pressures and depressed \( \dot{P}_{\text{max}} \) (table 1C).

The patients were 2, 14, 15, and 20 years old. The 2-year-old had a large residual ventricular septal defect with a 60% left-to-right shunt following tetralogy of Fallot surgery and was clinically in heart failure with tachypnea, tachycardia, hepatomegaly, and ascites. He was taking a diuretic. The 15-year-old had a double outlet right ventricle with severe pulmonic stenosis after bilateral Blalock-Taussig shunt procedures. The 20-year-old had tricuspid atresia after a Glenn shunt and a Blalock-Taussig shunt. These two patients were clinically not in heart failure and were not receiving any cardiotonic agents. The 14-year-old was in severe congestive heart failure and was felt to have a cardiomyopathy, as no anatomic defects were noted at catheterization. Unlike all the other patients, this patient was being maintained on dopamine 10 µg/kg/min and nitroprusside 0.6 µg/kg/min during the study.

The qualitative characteristics of the force-interval curves of these patients were distinctly different from
those in groups 1 and 2. The force-interval curves from the 2-year-old, 15- and 20-year-old patients in group 3 were biphasic, in contrast to the monophasic curves obtained from groups 1 and 2. The first-stage curve rose for small values of \( t \), and then, rather than plateauing, declined for larger values of \( t \) (the "droop", figs. 4 and 7). This droop was more pronounced the longer the basic interval, but it was also seen in the youngest patient, who could only be paced at basic intervals of 350-400 msec. (fig. 7). The fourth patient, the 14-year-old who was in severe congestive heart failure, did not demonstrate a biphasic curve. However, the pharmacologic effects of her supportive therapy on the force-interval relationship is uncertain.

Another unique feature of the patients in group 2 was the way the force-interval ratio depended on the test interval, \( t \). In two of the patients, the 2-year-old and 20-year-old, the ratio was less than one at the shortest \( t \). This postextrasystolic depression was seen only in the group 3 patients. As \( t \) was increased, the ratio increased (fig. 8). For all patients in groups 1 and 2 the ratio declined monotonically with increasing \( t \), except rarely for very short \( t \) (fig. 3). For all the patients in group 3 the ratio either began below 1.0 with the shortest \( t \) and increased monotonically to reach 1.0 with increasing \( t \) (fig. 8 \( t_0 = 350 \) msec) or changed biphasically, beginning at or below 1.0 and increasing for increasing \( t \) to exceed a ratio of 1 and declining for further increases in \( t \) (fig. 8 \( t_0 = 400 \) msec). Compare these curves in figure 8 with those in figure 5 from a 4-year-old, post tetralogy of Fallot with a small residual ventricular septal defect, whose echocardiographic measurements placed him in group 1.

The declining phase or "droop" of the force-interval curve did not appear to result from the heart operating near the peak of its length-tension relationship and, with progressive ventricular filling, on the descending limb. This possibility was excluded by the observation that the small natural beat-to-beat variations in EDD always accompanied a parallel variation in \( P_{\max} \). Increased EDD enhanced \( P_{\max} \). Furthermore, during the second stage curves \( P_{\max} \) increased with increasing EDD beyond that of the regular systole (fig. 4).

The possibility that the droop in the curve might have been the result of an extraordinary drop in the aortic pressure during the pause between trains (caus-
ing premature opening of the aortic valve and a less-
than-maximal value of $P_{\text{max}}$) was more difficult to ex-
clude. We did not simultaneously measure the aortic 
pressure in these patients during the two-stage experi-
ment. However, the increase in $P_{\text{max}}$ with increases in 
extorsystole noted in the second-stage curves in figure 4 would 
suggest this was not the case.

Discussion

Changes in heart rate and the introduction of a 
premature systole or extrasystole have about the same 
effect on the contractility of the human heart as on 
hearts of other mammals: an increase in rate poten-
tiates contractility, at least transiently, and an ex-
trasystole potentiates the next systole. The amount of 
postextrasystolic potentiation for a given test interval 
(i.e., coupling interval) differs from species to species, 
but the general features of the force-interval 
relationship seem to be common to all mammalian 
heart muscle (with the possible exception of rat heart). 
We summarize some of the general properties of the 
force-interval relationship that can be drawn from 
previous and present studies.\textsuperscript{1-7, 23-27}

1) $F_{\text{max}}$ (the maximum rate of rise of force) is a 
preferred measure of the force-interval relationship 
for isometric cardiac muscle. The following properties 
hold for the curves of $F_{\text{max}}$ (but not necessarily peak 
tension) vs test interval. $P_{\text{max}}$ (the maximum rate of 
rise of left ventricular pressure) is the equivalent 
measurement in the whole heart.

2) $F_{\text{max}}$ ($P_{\text{max}}$) increases monotonically with test 
interval, $t_1$ or $t_3$, for both the first stage and the second-
stage curves; the curves rise steeply for small values of 
the test interval, much more gradually during the 
plateau for large intervals. The plateau is higher for 
the second- than for the first-stage curves. The force-
interval ratio (the height of the second-stage plateau 
relative to the height of the first-stage plateau or $F_{\text{max}}$ 
($P_{\text{max}}$) of the last regular beat) depends on the basic 
cycle length, $t_0$, and on $t_1$. For a fixed value of $t_0$, the 
force-interval ratio decreases when $t_0$ is decreased, and 
at a fixed stimulus rate the ratio declines when $t_1$ is in-
creased. Three important exceptions of these 
generalities are discussed below.

3) The force-interval curves are scaled by a change 
of muscle length in the isolated muscle and by a 
change in volume in the intact heart.

4) The shape of the force-interval curves and the 
force-interval ratio change when the muscle is exposed 
to an inotropic agent. The modified shapes are in-
dependent of muscle length as described in (3) above. 
Thus the shape of the curve can be taken to be a 
measure of the inotropic state of the muscle.

5) The onset of hypertrophy modifies the shape of 
the force-interval curves and the force-interval ratio, 
and the modified shapes are also independent of mus-
cle length. Thus, hypertrophy can be viewed as a 
change in inotropy of the heart.

These general properties apply, where they have 
been tested, to the force-interval relationship of the 
conscious patient. Of special interest are the reports 
that reveal or suggest differences in postextrasystolic 
potentiation between patients with or without abnor-
mal left ventricle. Schwartz et al.\textsuperscript{9} and Van Der Werf 
et al.\textsuperscript{11} found a lack of potentiation in some patients 
with extensive coronary artery disease. However, 
Kvasnicka et al. demonstrated patients with car-
diomyopathies to have an enhanced amount of poten-
tiation when compared to patients who were normal 
or had atrial septal defects.\textsuperscript{10}

The sensitivity of the relationship to changes in in-
otropy, and in particular to the development of heart 
disease, stimulated us to undertake the present quan-
titative analysis of the force-interval relationship in 
man. As Schwartz et al.\textsuperscript{9} in their patient study pointed
out, the basic pacing rate must be the same if the patient's results are to be compared one to the other. Furthermore, all the investigations in man that were concerned with isovolumic indices have recognized the importance of the coupling interval between the last regular beat and the extra systole, t1, and have used various techniques to correct for the patient's data usually being obtained over a range of t1's. When the heart rates, t0, are not initially comparable, such corrections may further blur the results from one patient to another. In the present study we paced the atria with trains of stimuli delivered at a controlled rate and followed by test stimuli at controlled times. Although atrioventricular conduction time and refractoriness limited the ranges of t0, t1, and t2, we considered atrial stimulation preferable to bypassing the atrioventricular node and stimulating the ventricle directly because of the well-known effects on Pmax produced by ectopic pacing.28 Force-interval ratios from different patients were compared only if the basic and test intervals were the same. Timing was not the only factor that determined Pmax of the test systole and the shape of the force-interval curves. The time course of ventricular filling after the last regular systole in the train also affected the shape of the curves. Previous investigators have used the end-diastolic pressure as a gauge of the end-diastolic dimension. In some of the studies (Kvasnicka et al.10 and Schwarz et al.4) the compensatory pauses were probably long enough to allow preload to increase beyond that of the previous systole and so affect postextrasystolic potentiation (fig. 6a). Van Der Werf et al.11 used test intervals, t2, equal to t1 + t0. Our results indicate that the EDD of their test systole equalled that of the regular value. In the present study ventricular filling during the pause was monitored by imaging the minor axis of the left ventricle using echocardiography. The EDD was taken as the measurement of preload for the regular and test systoles. During the second stage of the experiment, EDD of the test systole, s2, frequently exceeded the EDD of the regular systole when t2 was greater than the basic interval, t0 plus t1. However, we could almost always find test systoles during the plateau phase that had EDDs equal to the regular value even when t2 was less than t1 + t0. Ventricular filling would increase the slope of the curve if the heart was operating on the ascending limb of the Frank-Starling curve and decrease the slope if it were on the descending limb. In practice, we could always tell if a given heart was operating on the ascending or the descending limb by examining the small train-to-train variations in EDD and Pmax of the last systole of the train. Invariably, in these beat-to-beat changes a larger value of EDD accompanied a larger value of Pmax and smaller EDD accompanied a smaller Pmax. Thus, all the hearts studied were operating on the ascending limb of the Frank-Starling relationship.

A "true" or isometric force-interval relationship like the one in figure 3C could have been constructed for every patient by correcting each value of Pmax according to the Pmax-EDD relationship of the heart. This was not done routinely, however, since our primary goal — the characterization of the force-interval relationship of each group of patients — could be carried out by simply measuring the force-interval ratio for various rates and test intervals.

The second factor that can sometimes distort the force-interval curves is the fall in the diastolic aortic pressure during the pause. If the pressure falls too low the valve will open before dP/dt has had time to reach its maximum value. The falling aortic pressure, if it fell to a low enough value, would reduce the plateau slope of the force-interval curve. The fall in aortic pressure was greatest and most likely to be important after a mechanically ineffective systole. However, even here the effect was negligible on the early part of the curve, for t2 less than two basic cycle lengths. When monitoring the systemic arterial diastolic pressure, Van Der Werf et al.11 noticed a decrease in the diastolic pressure for coupling intervals comparable to ours but found it to be slight, e.g., 10 mm Hg. In the study by Kvasnicka et al.,10 where the compensatory pause was longer so that two basic cycle intervals occurred before the introduction of the postextrasystolic beat, a larger drop in diastolic aortic pressure was noted. Therefore, it appears that the effects of diastolic aortic pressure on the value of Pmax during the plateau phase of the second stage curve may have been avoided. The diastolic aortic pressure fall found by Van Der Werf et al. and us was smaller than the 30 mm Hg found to alter Pmax in patients.22 An additional modifying effect on Pmax is the presence of a ventricular septal defect. In all three groups there were patients with different size ventricular septal defects, including restrictive ventricular septal defects. When there is a restrictive ventricular septal defect there is a pressure gradient between the two ventricles. Although it was anticipated that this systolic unloading might have produced confusing or complex results, this did not occur. This problem could be anticipated in the presence of other abnormalities not encountered in our study, such as mitral insufficiency or ventricular aneurysm.

A third factor that can change the shape of the force-interval curves is the state of mind of the patient. Some patients — especially the younger ones — became agitated when the catheter was inserted or when the echocardiographic transducer was positioned on their chest. We could not always prevent this reaction or allay it when it occurred. A fundamental concern was that an increase in sympathetic tone would do more than accelerate the heart rate and potentiate Pmax. Norepinephrine modifies the shape of the force-interval curves.19,20 Consequently, we did not pool the data from two patients who experienced extreme acceleration of heart rate (> 50%) and could not be calmed.

The differences between groups 1 and 2 and the relationship between the force-interval ratio and the echocardiographic ventricular wall thickness are in line with an earlier study. When we induced hyper-
trophy of the right ventricle of cats by banding the pulmonary artery, the ventricular wall mass increased, but the force per unit area and the maximum rate of rise of force per unit area were the same for papillary muscles from the normal and hypertrophied hearts; nevertheless, the force-interval ratios were significantly larger for the hypertrophied than for the normal group. This appeared to be the stable or second stage of hypertrophy described by Meerson.80 The underlying basis of these effects and similar effects found by Kvasnicka81 are uncertain. The potential effects of changes in cell size, cell surface-to-volume ratio, mitochondrial metabolism, or myofilament structural changes, are all possible causes for such a change in postextrasystolic potentiation.

Regardless of the cellular mechanisms, these results do point out the success in using simply the force-interval ratio for comparing one patient to a group or to another patient. Although these ratios do not describe the entire force-interval curve, they certainly provide a quantitative description of the amount of potentiation produced by a given t1 at a given t0.

The results from the force-interval curves from the patients in group 3 were biphasic and revealed postextrasystolic depression or no potentiation following short t1 intervals, in marked contrast to the monotonic curves and the greatest postextrasystolic potentiation following short t1 intervals obtained from patients in group 1 and group 2, and the patients described by Palmero and Caeiro82 in their statistical analysis of postextrasystolic potentiation in the human left ventricle. As we pointed out above, the droop in the curve did not result from the ventricle filling beyond the peak of the length-tension relationship (fig. 4); nor was it likely that a precipitous fall in the diastolic aortic pressure was the cause of the droop.

We are aware of three other cases of drooping of the force-interval curves: amphibian myocardium normally exhibits this kind of decline. This may not be relevant, however, since the force-interval relationship of amphibian hearts is qualitatively different from that of the mammalian heart.83 Droops can be induced in normal mammalian heart muscle by exposure to large doses of norepinephrine13 or isoproterenol.29 This suggests that the local norepinephrine release of the patients in group 3 might have been unusually high, and in the case of the 14-year-old patient maintained on dopamine, that the therapeutic procedure might have altered the force-interval relationship. The previously described low concentrations of nor-epinephrine in myocardium from patients in heart failure coupled with elevated urinary norepinephrine excretion in such patients may be relevant here.31,32 A third case suggests that the droop in the curve might reflect an inotropic change in the muscle secondary to or preceding heart failure. Preliminary experiments on papillary muscles from cats with heart failure induced by banding of the pulmonary artery (unpublished results) gave similar results: the first- and second-stage curves had the same kind of droop as the patients in group 3; that is, Fmax rose from a small value to a plateau and then fell with increasing t1 to equal Fmax of the last regular beat. The underlying etiology of this unusual property is not known. However, the droop was not blocked by propranolol as was the catecholamine-induced droop.

Summary

We have carried out a quantitative analysis of the force-interval relationship of the human left ventricle and compared it to previous studies done in both intact subjects as well as isolated muscle. The characteristics of the force-interval relationship of the normal patient resembled those of normal isolated mammalian muscle (except when exposed to high levels of catecholamines). The relationship in group 2 (patients with increased left ventricular dimensions and normal pressure indices) resembled those obtained from isolated muscles from hypertrophied hearts. The relationship from group 3 (patients with increased left ventricular EDDs and depressed pressure indices, two of whom were in clinical heart failure) resembled those induced in normal muscles exposed to high levels of catecholamines, and those obtained from experimentally induced heart failure. The force-interval relationships of the four patients who fell into the third group were strikingly different from the other groups. This suggests that the force-interval relationship may be useful to describe changes in the inotropic state of the patient's heart.

References

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