

## The Contractile Properties of Human Heart Muscle: Studies on Myocardial Mechanics of Surgically Excised Papillary Muscles \*

EDMUND H. SONNENBLICK,† EUGENE BRAUNWALD, AND ANDREW G. MORROW

(From the Cardiology Branch and the Clinic of Surgery, National Heart Institute, Bethesda, Md.)

Previous studies of the performance characteristics of the heart have usually been directed to its function as a pump and, therefore, have been concerned principally with measurements of intravascular and intracardiac pressures, flows, and derivatives of these variables. Over the past three decades, extensive studies of skeletal muscle have provided an understanding of the mechanical behavior and energetics of this tissue (1-5). Recent studies of isolated segments of mammalian heart muscle (6-8) have permitted extension of this approach to the myocardium and have suggested the feasibility of analyzing the performance of the ventricle in terms of its properties as a muscle (9-12). Although efforts have been made to characterize normal and abnormal function of the human heart from this point of view (13-15), a necessary first step is a detailed description of the mechanical properties of human heart muscle. Such a description is presented in this report, and a direct extension of these investigations to the intact human ventricle is the subject of the companion paper (16).

### Methods

Left ventricular papillary muscles were obtained at the time of mitral valve replacement in 19 patients. The patients ranged in age from 21 to 64 years; 13 were males and 6 were females. The major hemodynamic abnormality in 8 patients was mitral regurgitation, in 5 patients it was mitral stenosis, and in 6 patients combined stenosis and regurgitation were present. Five patients had associated aortic valve disease, and in 4 of the 19 patients the aortic valve was also replaced with a prosthesis

\* Submitted for publication December 28, 1964; accepted February 25, 1965.

Presented in part before the American Society for Clinical Investigation, May 4, 1964, Atlantic City, N. J.

† Address requests for reprints to Dr. Edmund H. Sonnenblick, National Heart Institute, Bethesda, Md. 20014.

at the same operation. The valvular malformation resulted from rheumatic heart disease in 18 patients, and in the other mitral regurgitation was caused by ruptured chordae tendineae with an otherwise normal valve. All of the patients were in functional class III or class IV and were receiving maintenance digoxin therapy at the time of operation.

The mitral valve was exposed during total cardiopulmonary bypass, and after the valve leaflets had been detached from the annulus, the papillary muscles were divided at their origins from the ventricular wall and the valve and muscles removed en bloc. The patients' temperatures were usually 34 to 35° C, and bypass had been in progress for 10 to 15 minutes when the papillary muscles were transected. Immediately upon removal, the papillary muscles were placed in Krebs solution into which a 95% O<sub>2</sub> and 5% CO<sub>2</sub> gas mixture was bubbled. The thinnest discrete segment of papillary muscle was then selected and rapidly transferred to a myograph. If the papillary muscles were unduly thick, they were split longitudinally to provide a thin segment and to facilitate oxygenation. The lengths of the muscle segments, at the peak of the length-active tension curve, averaged 14.0 ± 3.9 (SD) mm, whereas the cross-sectional areas averaged 5.5 ± 3.9 mm<sup>2</sup>.

The myograph in which the muscles were studied has previously been described in detail (7). The papillary muscle was held at its lower nontendinous end by a spring-loaded clip, forming the end of a rigid pin that penetrated the bottom of the bath and was directly attached to a Statham (GI-4-250) force transducer. The upper tendinous end of the muscle was attached to an isotonic lever for the measurement of muscle shortening, and the lever itself was mounted on a rigid Palmer stand. With this arrangement, when the position of the lever was fixed, the force of isometric contraction at any desired muscle length could be measured. The lever could also be freed and, by appropriate loading, the extent and velocity of shortening of the muscle at any preload (the small load that acts on the resting muscle and thereby establishes the initial length) and afterload (the load encountered by the contracting muscle when it attempts to shorten) could be measured. The muscles were stimulated supermaximally with square wave DC impulses of 5 msec duration,<sup>1</sup> delivered through large platinum plates placed

<sup>1</sup> American Electronics stimulator, model 104A.

parallel to the long axis of the muscle. Force, muscle length, the first derivatives of these variables, and the stimulus artifact were recorded on a multichannel oscillograph, and in some instances the transducer outputs were displayed on a dual-beam oscilloscope (Tektronix model 502) and photographed. The work performed by the papillary muscle was calculated as the product of afterload in grams and displacement in millimeters, and was expressed in units of gram-millimeters; maximal power was calculated as the product of the maximal shortening rate ( $dl/dt$ ) and afterload, and it was expressed in units of gram-millimeters per second.

Experiments were carried out at 30° C. In order to maintain optimal performance of the muscles for prolonged periods of time, frequencies of contraction of 6 to 12 per minute were employed, except when the effects of changes of frequency of contraction were specifically studied. To assure steady-state performance, a period of 1 hour was allowed between the time the muscle was placed in the myograph and the initial recordings. Each study was terminated when mechanical performance began to deteriorate. Papillary muscles from three additional patients did not maintain a steady state at the onset of the experiment and were discarded.

Four major aspects of myocardial mechanics were analyzed: 1) the passive and active length-tension curves, 2) the force-velocity relation of the contractile component of the muscle, with considerations of external work and power, 3) the load-extension ("stress-strain") relation

of the series elastic component, and 4) the relationship between the frequency of contraction and the performance of the muscle, as reflected in force development, velocity of shortening, work, and power. The effects of the cardiac glycoside strophanthidin and of norepinephrine on the force-velocity relation of the muscles were also determined.

## Results

*I. Length-tension relations.* Isometric length-tension curves were determined in the papillary muscles from all 19 patients, and the results of a typical experiment are shown in Figure 1A. In order to allow comparisons among different experiments, all length-tension curves were performed at 30° C at a frequency of 12 contractions per minute. The actively developed tension was calculated as the difference between the peak systolic (total) tension and the resting tension, and that muscle length at which both the resting and active tensions approached zero was defined as  $L_0$  (Figure 1A). As muscle length was increased, both active and resting tensions rose; the peak of the length-active tension curve was reached when the muscle was stretched to an average length of  $151 \pm 11\%$  of  $L_0$ , and the maxi-

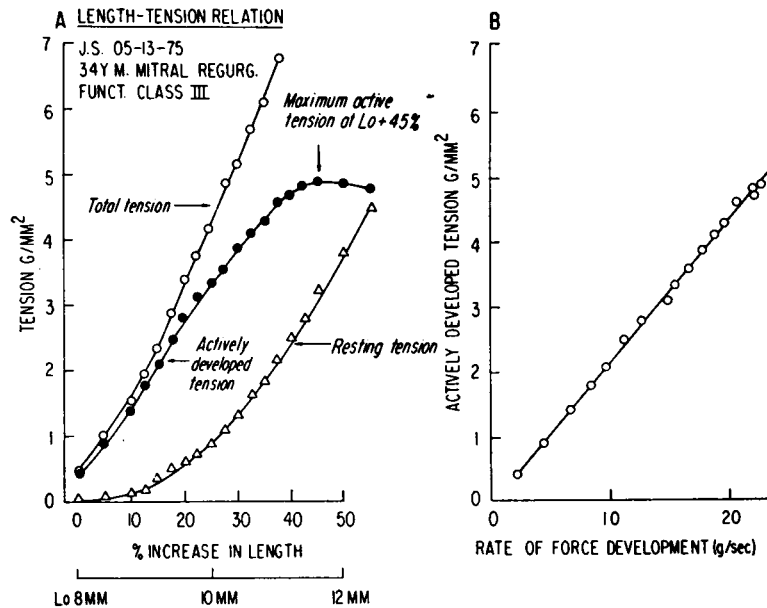


FIG. 1. A. LENGTH-TENSION RELATIONS OF HUMAN PAPILLARY MUSCLE. Abscissa: Muscle length in millimeters and the per cent increase in muscle length above  $L_0$  (muscle length at which both the resting and active tensions approached zero). Frequency of contractions = 12 per minute. Cross-sectional area of muscle = 3.6 mm<sup>2</sup>. B. RELATIONSHIP BETWEEN ACTIVELY DEVELOPED TENSION AND THE MAXIMAL RATE OF ISOMETRIC FORCE DEVELOPMENT.

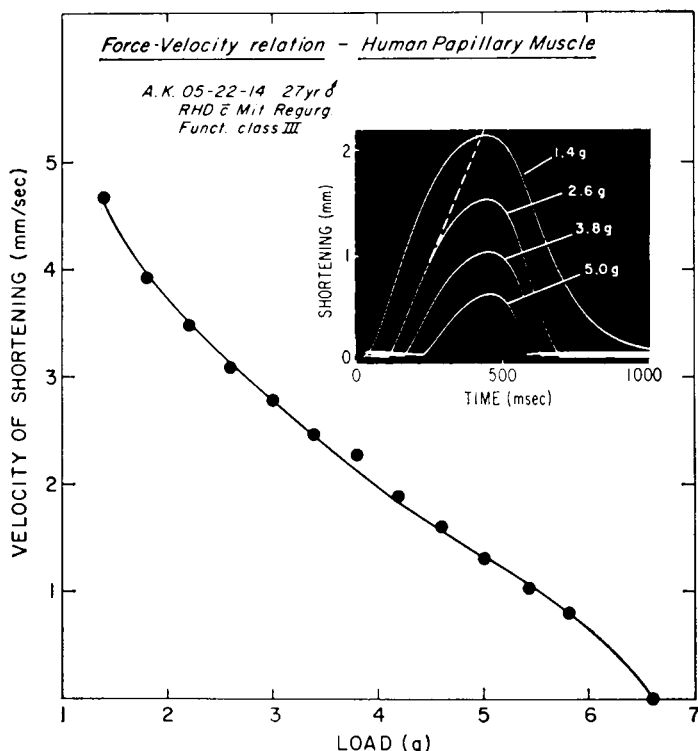


FIG. 2. RELATION BETWEEN INITIAL VELOCITY OF ISOTONIC SHORTENING AND AFTERLOAD. Frequency of contractions = 12 per minute. Muscle cross-sectional area = 3.2 mm<sup>2</sup>. Preload = 1.4 g with a muscle length of 15 mm. The insert in the upper right shows several oscillographic recordings from which the experimental points were calculated, and the afterload for each of these contractions is indicated.

mal actively developed tension averaged  $1.81 \pm 1.19$  (SD) g per mm<sup>2</sup>. With further increases in muscle length, actively developed tension reached a plateau and then declined as resting tension rose precipitously. The time interval from the onset of contraction to the instant at which peak tension was achieved was independent of muscle length and, as a consequence, when muscle length was increased the maximal rate of force development ( $dp/dt$ ) was found to be a linear function of actively developed tension (Figure 1B). No correlation between maximal developed tension per unit cross-sectional area and the actual cross-sectional area of the muscle could be perceived.

II. *Force-velocity relations.* Force-velocity relations were determined in the papillary muscles of seven patients. A typical curve is depicted in Figure 2, and in the insert some of the original oscillographic tracings from which the curve was derived are reproduced. The initial length of

the muscle was set by a small preload, which was maintained constant for the entire curve. The effects on the velocity of shortening of progressively increasing afterload were then determined. The maximal velocity of shortening ( $V_{max}$ ) could not be determined directly at zero load, since a small preload was necessary to establish the initial muscle lengths, and  $V_{max}$  was, therefore, obtained by extrapolation. An inverse relation between the afterload and both the initial velocity and extent of shortening was observed in every muscle. It was also noted that the time from the stimulus to maximal shortening was independent of the afterload.

The effects of altering the initial muscle length on the force-velocity curve were examined by determining 32 curves in 4 muscles. As seen in Figure 3A,  $V_{max}$  appeared to remain constant, but  $P_0$  (isometric tension) increased as a function of initial length.  $P_0$  is used in this context as

isometric force without implying tetanic force as would be obtained in skeletal muscle. The effects of altering the frequency of contraction on the force-velocity curve were examined by determining 13 curves in three muscles (Figure 3B). In individual muscles, contraction frequencies were varied between 6 and 60 per minute, but all three muscles were examined at rates of 12 and 30 per minute. When the frequency of contraction was increased at a constant initial muscle length,  $P_0$  remained essentially unchanged, while  $V_{max}$  increased strikingly. For the three muscles examined,  $V_{max}$  was 38%, 39%, and 23% greater at 30 contractions per minute than at 12 contractions per minute.

The effects of strophanthidin (0.5  $\mu\text{g}$  per ml) on the force-velocity relation were studied in the muscles obtained from three patients, and a representative pair of curves is shown in Figure 4A.

The glycoside augmented both  $P_0$  (39%, 20%, and 84%, respectively) and  $V_{max}$  (15%, 140%, and 125%, respectively) in each muscle. Norepinephrine (0.2  $\mu\text{g}$  per ml) also shifted the force-velocity relation upwards and to the right (Figure 4B); norepinephrine augmented  $P_0$  by  $24\% \pm 6\%$  in the 14 muscles examined. In contrast to the effects of changing initial muscle length, the shift in the force-velocity relation resulting from either norepinephrine or strophanthidin was always accompanied by a decrease in the time from stimulation to maximal force development. This time interval decreased from an average of 725 msec to 660 msec with strophanthidin, and from an average of 720 msec to 530 msec with norepinephrine.

Inspection of the force-velocity relation indicates that as  $V_{max}$  and  $P_0$  are approached, external work and power approach zero, and these two

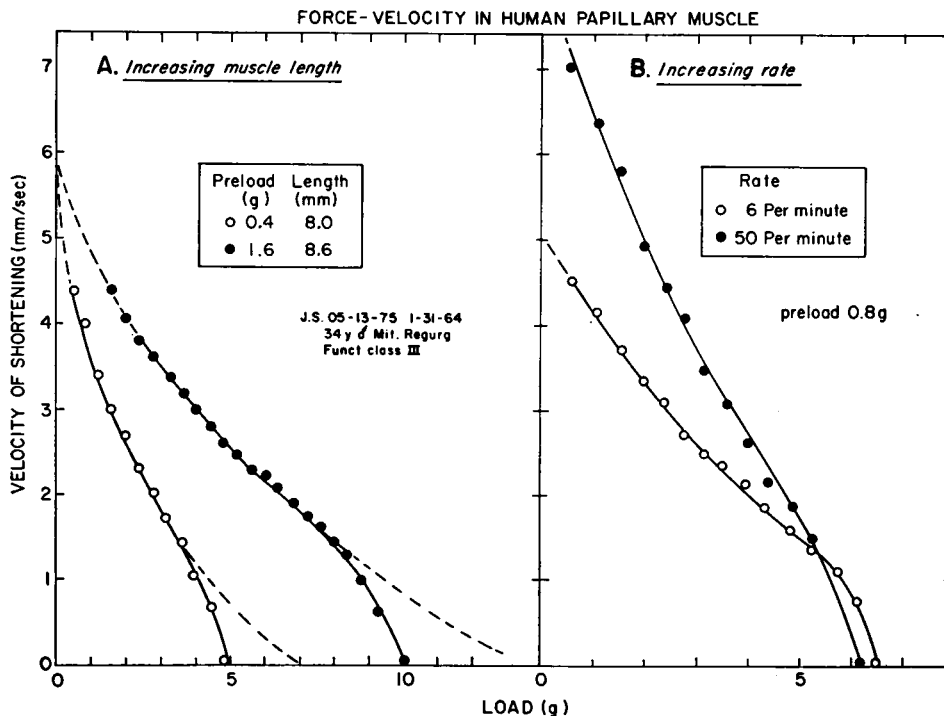


FIG. 3. A. EFFECTS OF INCREASING INITIAL MUSCLE LENGTH ON THE FORCE-VELOCITY RELATION. The maximal isometric force ( $P_0$ ) is augmented without a change in maximal velocity of shortening ( $V_{max}$ ). The time from stimulus to peak shortening was 440 msec for both initial lengths. Frequency of contractions = 12 per minute. B. EFFECTS OF INCREASING FREQUENCY OF CONTRACTION FROM 6 PER MINUTE TO 50 PER MINUTE.  $V_{max}$  is increased without a change in  $P_0$ , while the time from stimulus to peak shortening decreased from 420 to 280 msec. The curves in A and B were derived from the same muscle, which had a cross-sectional area of  $3.6 \text{ mm}^2$ .

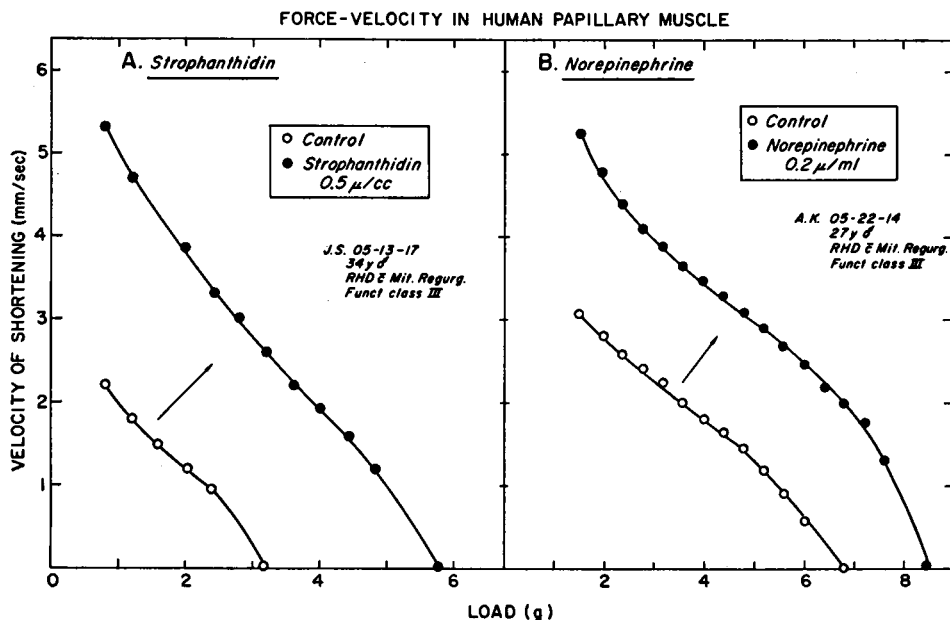


FIG. 4. A. EFFECT OF THE ADDITION OF STROPHANTHIDIN ON THE FORCE-VELOCITY RELATION. Initial muscle length = 10.0 mm with a preload of 0.8 g. Muscle cross-sectional area = 3.6 mm<sup>2</sup>. The addition of strophanthidin increased both  $V_{max}$  and  $P_0$  while decreasing the time from stimulation to maximal shortening from 390 to 340 msec. B. EFFECT OF THE ADDITION OF NOREPINEPHRINE ON THE FORCE-VELOCITY RELATION. Initial muscle length = 15.0 mm with a preload of 1.4 g. Muscle cross-sectional area = 3.2 mm<sup>2</sup>. Norepinephrine augmented both  $V_{max}$  and  $P_0$  while decreasing the time from stimulation to peak shortening from 730 to 540 msec.

variables reach a maximal value at some intermediate load. In the seven muscles in which force-velocity curves were obtained, it was observed that the peak values of work were achieved with afterloads that ranged from 45% to 55% of isometric force ( $P_0$ ), while the peak values of maximal power were achieved with afterloads ranging from 50% to 60% of the isometric force ( $P_0$ ). Increasing initial length of the muscle elevated the afterload-work and afterload-power curves and raised the afterload at which the peak values of work and power were achieved (Figure 5, A and B). At a constant initial muscle length the addition of norepinephrine also elevated and shifted the load-work and load-power curves to the right (Figure 5, C and D). Increasing the frequency of contraction did not significantly affect the load-work curve in the three muscles examined (Figure 5E). However, in all instances a significant elevation of the load-power curves resulted from increasing frequency (Figure 5F), peak power rising by 40%, 28%, and 22%, respectively, in the three muscles as fre-

quency of contraction was elevated from 12 to 30 per minute.

III. *Load-extension curve of the series elastic component.* The series elastic component of the papillary muscles was characterized in muscles from 5 patients by an analysis of afterloaded isotonic contractions relative to time after stimulation. In Figure 6A a typical force-velocity curve is shown, whereas in Figure 6B the velocities of shortening ( $dl/dt$ ) and the force for the same contractions are plotted as functions of the time after stimulation. As described in detail elsewhere (17), at the time the muscle stops developing force and begins to shorten, the series elastic component is being stretched at a velocity ( $dl/dt$ ) equal to but opposite in direction to that of the contractile element. Therefore, the curve relating  $dl/dt$  to time after stimulation (Figure 6B) applies to both the contractile element and the series elastic component. By integrating  $dl/dt$  as a function of time, the extension of the series elastic (SE) component with increasing force (load) was determined ( $\Delta L$  of SE =  $\int_{P_0}^F P_0$

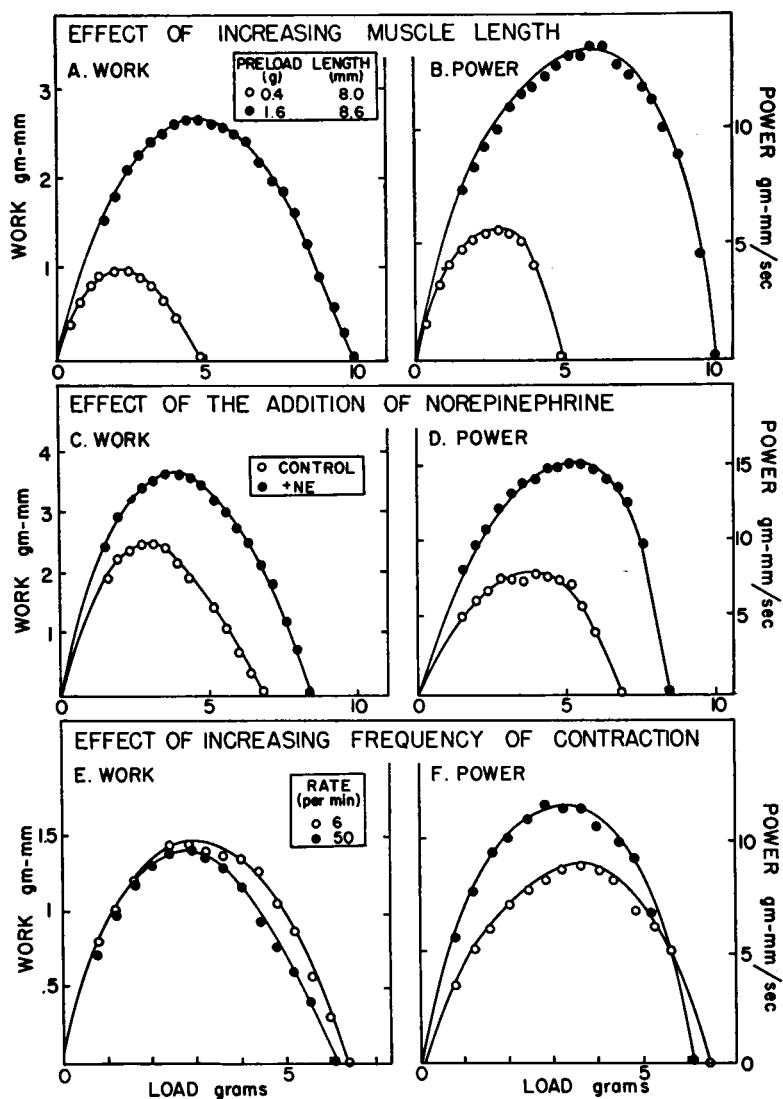


FIG. 5. RELATIONS OF WORK AND POWER WITH INCREASING AFTERLOAD, AS INITIAL MUSCLE LENGTH WAS CHANGED (A AND B), NOREPINEPHRINE WAS ADDED (C AND D), AND THE FREQUENCY OF CONTRACTION INCREASED (E AND F).

$dl/dt \cdot dt$ ). The load-extension curve of the series elastic component obtained in this manner is reproduced in Figure 6C, and shows that with progressive extension of the series elastic the force developed increased exponentially. In the five muscles in which this analysis was carried out, it was observed that during an isometric contraction the series elastic was stretched by  $8.4\% \pm 0.5\%$  of the initial length of the muscle at which the force-velocity curve was obtained. Further, the load-extension curve of the series

elastic component was not altered by changing frequency of contraction nor by the addition of norepinephrine or strophanthidin.

IV. *Force frequency relations.* The effects of changing frequency of contraction were studied in papillary muscles obtained from 16 patients. A representative study on a muscle relating frequency to extent of shortening, time to maximal shortening, and velocity of shortening is shown in Figure 7A, whereas a representative study on an isometrically contracting muscle relating fre-

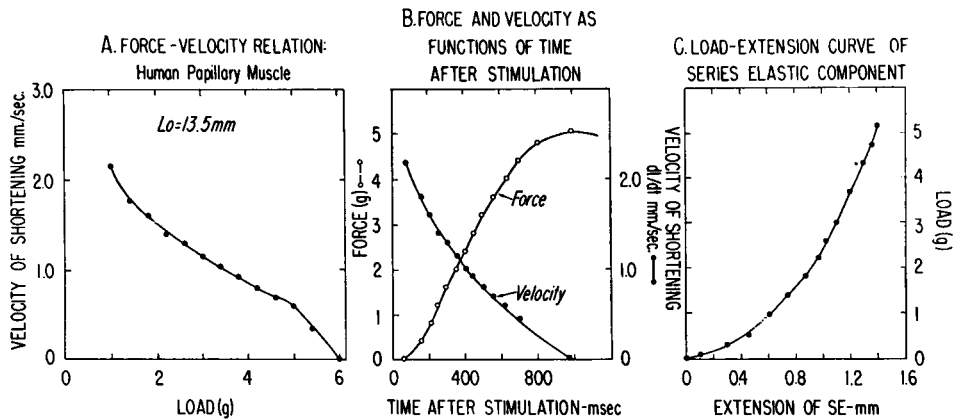


FIG. 6. PROPERTIES OF THE SERIES ELASTIC COMPONENT OF A HUMAN HEART MUSCLE WITH AN INITIAL MUSCLE LENGTH OF 13.5 MM AT A PRELOAD OF 1.0 G. Muscle cross-sectional area = 3.5 mm<sup>2</sup>. A. Velocity of isotonic shortening in millimeters per second as a function of increasing afterload. B. Velocity of shortening and force of contraction as functions of the time after stimulation of the muscle. C. The load-extension relation of the series elastic component.

quency to isometric force, time to peak force, and rate of development of force is shown in Figure 7B. At a frequency of 6 contractions per minute, the time from the onset of contraction to peak tension averaged 876 ± 150 msec, while the rate of force development averaged 20.8 g per second. At a frequency of 50

contractions per minute, the time to peak tension decreased in every muscle to an average of 455 ± 89 msec, whereas the maximal rate of force development increased in every muscle to an average value of 35.0 g per second. Similarly, in every muscle the time to peak shortening decreased from an average of 410 ± 48 msec to

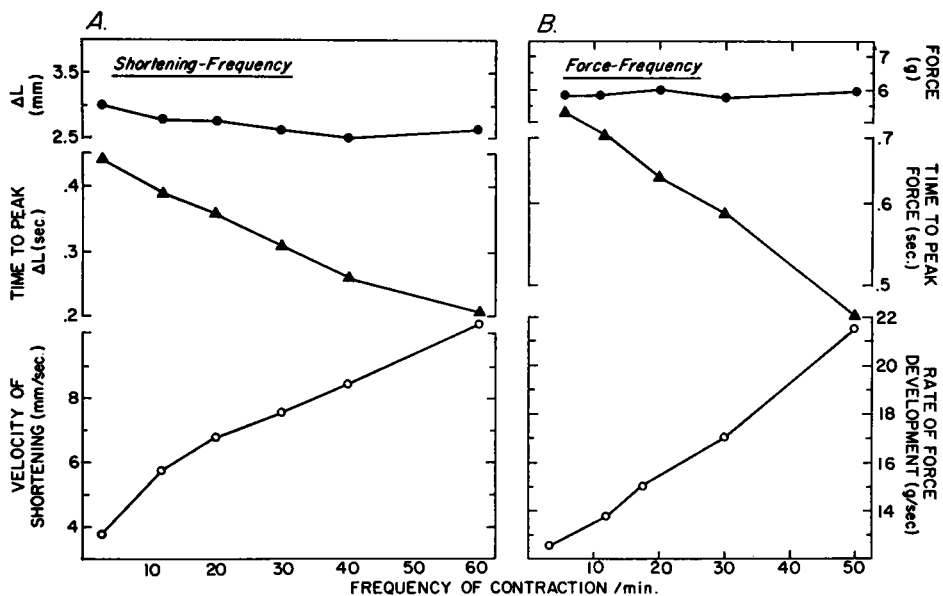


FIG. 7. A. VELOCITY OF SHORTENING, THE EXTENT OF SHORTENING ( $\Delta L$ ), AND THE TIME FROM STIMULATION TO PEAK SHORTENING ARE SHOWN AS FUNCTIONS OF FREQUENCY OF CONTRACTION. Preload = 0.4 g; afterload = 2.0 g. Muscle length = 15.0 mm; cross-sectional area = 3.5 mm<sup>2</sup>. B. RELATION OF ISOMETRICALLY DEVELOPED FORCE, THE TIME FROM STIMULATION TO PEAK FORCE DEVELOPMENT, AND THE RATE OF FORCE DEVELOPMENT AS FUNCTIONS OF FREQUENCY OF CONTRACTION. Muscle length = 9.0 mm; cross-sectional area = 7.5 mm<sup>2</sup>.

$280 \pm 32$  msec, while the velocity of shortening increased in every muscle, from an average of  $4.63 \pm 0.57$  to  $6.58 \pm 0.42$  mm per second. On the other hand, alterations in frequency of contraction produced little change either in isometric force or in the extent of shortening of the isotonically contracting muscle. At 6 contractions per minute, force averaged 12.4 g and at 50 contractions per minute 10.4 g. In the isotonically contracting muscle the extent of shortening at these rates averaged  $1.85 \pm 0.27$  and  $1.79 \pm 0.22$  mm.

### Discussion

The left ventricular papillary muscles, which may be obtained from patients in the course of corrective cardiac operations, provide a unique opportunity for analyzing *in vitro* the contractile properties of human heart muscle. Since the preparation described in this report has not been employed previously, it is important to comment upon certain limitations inherent in its use. Perhaps the most important of these is the thickness of the human papillary muscle, which may not allow for adequate oxygenation at physiologic temperatures and frequencies of contraction. For this reason, most of the experiments described herein were carried out at  $30^{\circ}$  C and at 6 to 12 contractions per minute. Fortunately, it is possible to recognize inadequate oxygenation of the muscle in relation to its energy requirements since, when this occurs, the mechanical performance of the muscle deteriorates progressively. As noted previously, stable mechanical activity could not be achieved in several preparations, and these muscles were discarded. Similarly, even in muscles that were initially stable, the experiments were terminated when, in the course of the study, a decrease in performance was observed.

One meaningful way of characterizing a muscle's performance is to measure the isometric tension that it develops at the apex of the length-active tension curve. In order to compare different muscles, the maximal isometric tension is corrected for the muscle's cross-sectional area. Abbott and Mommaerts observed a peak tension of the order of 2.0 g per  $\text{mm}^2$  at  $30^{\circ}$  C in papillary muscles from normal cats (6). The average peak tension observed in the present study was

only slightly lower than 2.0 g per  $\text{mm}^2$ , and two muscles developed peak forces as high as 4.5 g per  $\text{mm}^2$ . It is of interest that the cross-sectional area of the muscle did not appear to influence the normalized maximal active tension. Furthermore, it must be appreciated that all of the muscles studied in this investigation were obtained from patients with serious organic heart disease, and on analysis many of these muscles were found to be depleted of norepinephrine (18). It is possible that the congestive heart failure state or norepinephrine depletion (19), or both, might have depressed the mechanical performance of certain muscles and thus account for the lower values of peak tension that were observed in them. The possible association of myocardial norepinephrine concentration to the mechanical performance of papillary muscles is presently under investigation.

The close resemblance between the length-active tension curves of the papillary muscle, studied *in vitro*, and the human ventricular myocardium, previously studied *in vivo* by means of a strain gauge arch (20), lends further support to the validity of the human papillary muscle preparation and indicates the relevance of the data obtained to the intact heart. The large elevations of tension that occur consequent to small increases in initial length (Figure 1) demonstrate the potential usefulness of the Frank-Starling mechanism when increases in force of contraction are required. From previous studies on intact patients, it may be inferred that the left ventricle of a subject without heart failure operates on the ascending limb of the Frank-Starling curve, but that the left ventricle of a patient with heart failure operates near the peak or along the plateau of the curve (21, 22). When these observations are taken together with the present findings that the peak of the length-active tension curve is reached at  $L_0 + 51\%$ , it would appear that the end-diastolic fiber lengths in the normal ventricle are less than this value, while the end-diastolic fiber lengths in the failing myocardium are probably close to this value. Inspection of Figure 1 also reveals that as the peak of the length-active tension is approached, the resting length-tension curve rises sharply. In this region of the curve not only is further augmentation of ventricular performance through the operation of the Frank-



Starling mechanism not possible, but even small increases in initial length require substantial elevations of ventricular filling pressure.

Extensive investigations of skeletal muscle (1-5) have made it clear that a more complete characterization of contraction requires a consideration not only of the force developed by the muscle, but also of its velocity of shortening. The relation between these two variables comprises the force-velocity curve. In skeletal muscle, this relation is generally examined under tetanic conditions, while in heart muscle tetanus cannot ordinarily be induced, and single contractions provide the basis of the force-velocity relations that are obtained. Previous investigations on the cat papillary muscle have demonstrated that, in contrast to skeletal muscle, the force-velocity curve of myocardium does not remain fixed but may be shifted by a variety of influences (6-8). If the duration of the active state of the contractile system is abbreviated, the force-velocity curve may deviate from its expected hyperbolic form, so that as the load is progressively increased, velocity falls off more rapidly than anticipated (Figures 2 to 4). The isometric tension that is actually recorded may be less than that which would have occurred if the active state had continued and the muscle had contracted tetanically. Factors tending to shorten the active state, such as increasing the temperature of the bath, exaggerated the deviation of the curve from a hyperbolic form at higher loads.

From the present study it is clear that an increase in initial muscle length increases the maximal force of isometric contraction ( $P_o$ ) without altering the maximal velocity of shortening ( $V_{max}$ ). It is suggested that this type of shift in the force-velocity curve does not represent a change in the fundamental contractile state of the myocardium, since it now appears that alterations in initial muscle length change the total number of active contractile sites, without affecting the rate of their interaction (4, 8, 17). It has also been shown that the force-velocity curve can be shifted by increasing the frequency of contraction (Figure 3) and by the administration of norepinephrine or strophanthidin (Figure 4). In contrast to the effects of altering initial muscle length, these interventions augment  $V_{max}$  (with or without elevating  $P_o$ ). It is suggested that this type

of shift in the force-velocity curve does represent a change in the fundamental contractile state of the myocardium, since it is believed that the elevation of  $V_{max}$  results from an increase in the rate of interaction of the contractile sites, regardless of the number of sites involved (4, 8). A. V. Hill has provided evidence for the view that the force-velocity relation represents a fundamental mechanical property of active muscle (1). This view, more recently expanded upon by Podolsky (4), derives from the observations made on the frog sartorius muscle that the rate of heat production depends on the velocity of shortening (1). It has been concluded that there is a tight link between the chemical processes that generate force and the mechanical events, and that a change in  $V_{max}$  (the intrinsic speed of the muscle) implies that a basic alteration has occurred in the mechanochemical coupling at the sites that generate force.

It is readily apparent that both the power and work performed by the muscle may be considered to be derivatives of the force-velocity relation. Just as the extent of shortening and the velocity of shortening are functions of the load, so are the products of shortening and load (work) and velocity of shortening and load (power). It is of interest that while an increase in the initial length of the muscle augmented both work and power at any given load, an increase in the frequency of contraction elevated the power but did not affect the work performed (Figure 6, E and F), since velocity of shortening increased without increasing extent of shortening (Figure 7). Similar observations have also been made in the intact dog heart (23). From these considerations it is apparent that a change in the contractile state of the muscle can occur and not be detected in the relationship between initial length and work, but be clearly apparent in the force-velocity and load-power relationships.

The effects of altering the frequency of contraction on the mechanical performance of heart muscle has been the subject of considerable interest and investigation. It is now clear that the force-frequency relation differs strikingly among various mammalian species and that even in the same species atrial and ventricular muscle may behave differently (24-26). Accordingly, it was not possible, on the basis of existing in-

formation, to predict the effects of altering frequency on the contractile properties of human heart muscle. It was observed that as the frequency of contraction was increased, the duration of contraction diminished and the velocity of shortening increased. An important consequence of this reciprocal relationship is the relative constancy of the force or extent of shortening observed, within the range of frequencies examined. Since force remained constant at increasing frequency, there was no evidence that the human myocardium exhibited the classical Bowditch or "force staircase" (27), but the profound augmentation of the velocity of shortening (Figure 7A) and increase of  $V_{max}$  in the force-velocity curve (Figure 3) indicate that this tissue does exhibit what might be termed a "velocity staircase." These data on the effect of frequency on the duration of contraction of the isolated human papillary muscle also help to explain findings in the intact heart. The abbreviation of contraction time with increasing rate is reflected in the shortening of the systolic ejection period and augmentation of the mean systolic ejection rate in the dog heart in which stroke volume is held constant (28). Similarly, the striking decrease in the systolic ejection period observed when heart rate is increased by electrical stimulation of the right atrium in human subjects can be accounted for primarily by the shortening of the contraction time (29). Despite these apparent correlations between the findings in the isolated muscle and in the intact heart with increasing frequency of contraction, certain limitations of the preparation must be kept in mind. The findings obtained in this investigation apply for frequencies below physiological levels, i.e., less than 50 contractions per minute. Further, these muscles have, by definition, been obtained from "failing" ventricles and from patients being maintained on digoxin. Thus, the applicability of the observed "velocity" staircase requires further confirmation.

Since the development of force by muscle requires the interaction of contractile elements with a series elastic component (1), an understanding of the mechanical properties of the latter is essential to an analysis of myocardial contraction. As the contractile element shortens, the series elastic component is extended. If the external ends of the muscle are fixed, i.e., in an isometric

contraction, the rate of force development by the muscle depends not only on the force-velocity relations of the contractile element, but also upon the stress-strain characteristics of the passive, springlike series elastic. Since the addition of norepinephrine to cat papillary muscle (8), and of both norepinephrine and strophanthidin to human muscle, does not alter the stress-strain characteristics of the series elastic component, it may be inferred that changes in the rate of force development are dependent primarily on performance of the contractile element. In the present investigation it was calculated that during isometric contractions the series elastic component is stretched by an average of 8.4% of the entire muscle length. Thus, it is apparent that significant shortening of the contractile elements occurs even during so-called isometric contractions. This observation is also relevant to an understanding of the discrepancy between the actual work performed by the contractile elements and the calculated external work performed by the isolated muscle of the intact heart, a fact that is receiving increasing attention in consideration of energy control in heart muscle (30).

### Summary

The contractile properties of human heart muscle were studied in left ventricular papillary muscles excised from 19 patients at the time of prosthetic replacement of the mitral valve. Analysis of the isometric length-tension relations revealed that the peak of the active tension curve was reached when the muscle was stretched to an average length that exceeded the initial length by 51%. Further increases in muscle length produced a precipitous rise in resting tension, while active tension declined. An inverse relation between afterload and initial velocity of shortening was observed in every muscle, extending to human heart muscle the concept of force-velocity relations. When initial muscle length was increased, isometric tension was augmented but the maximal velocity of shortening remained constant. The addition of strophanthidin or norepinephrine increased the maximal velocity of shortening as well as the isometric tension, whereas increasing the frequency of contraction augmented the maximal velocity of shortening only. It is suggested that

the contractile state of the myocardium can be described by the force-velocity relation.

An analysis of the series elastic component of the muscle indicated that the series elastic component was stretched an average of 8.4% during an isometric contraction, indicating that significant shortening of contractile elements occurs even in the absence of external muscle shortening. When the frequency of contraction was increased, the duration of contraction diminished, but the velocity of shortening increased reciprocally. The resultant force developed, or extent of shortening, remained relatively unchanged. Thus, at any given muscle length, the improved contractile state of the muscle resulting from increasing the frequency of contraction was reflected by the augmented power developed by the muscle, but was not evident in the external work performed.

These studies on the contractile properties of papillary muscles provide a framework for an analysis of the performance of the intact human myocardium in terms of fundamental muscle mechanics.

### References

- Hill, A. V. The heat of shortening and the dynamic constants of muscle. *Proc. roy. Soc. B* 1938, **126**, 136.
- Wilkie, D. R. Mechanical properties of muscle. *Brit. med. Bull.* 1956, **12**, 174.
- Jewell, B. R., and D. R. Wilkie. The mechanical properties of relaxing muscle. *J. Physiol. (Lond.)* 1962, **152**, 30.
- Podolsky, R. J. Mechanochemical basis of muscular contraction. *Fed. Proc.* 1962, **21**, 964.
- Hill, A. V. The effect of load on the heat of shortening of muscle. *Proc. roy. Soc. B* 1964, **159**, 297.
- Abbott, B. C., and W. F. H. M. Mommaerts. A study of inotropic mechanisms in the papillary muscle preparation. *J. gen. Physiol.* 1959, **42**, 533.
- Sonnenblick, E. H. Force-velocity relations in mammalian heart muscle. *Amer. J. Physiol.* 1962, **202**, 931.
- Sonnenblick, E. H. Implications of muscle mechanics in heart muscle. *Fed. Proc.* 1962, **21**, 975.
- Sonnenblick, E. H., and S. E. Downing. Afterload as a primary determinant of ventricular performance. *Amer. J. Physiol.* 1963, **204**, 604.
- Levine, H. J., and N. A. Britman. Force-velocity relations in the intact dog heart. *J. clin. Invest.* 1964, **43**, 1383.
- Fry, D. L., D. M. Griggs, Jr., and J. C. Greenfield, Jr. Myocardial mechanics; tension-velocity-length relationships of heart muscle. *Circulat. Res.* 1964, **14**, 73.
- Downing, S. E., and E. H. Sonnenblick. Cardiac muscle mechanics and ventricular performance: force and time parameters. *Amer. J. Physiol.* 1964, **207**, 705.
- Gorlin, R., E. L. Rolett, P. M. Yurchak, W. C. Elliott, F. J. Lane, and R. H. Levy. Left ventricular volume in man measured by thermodilution. *J. clin. Invest.* 1964, **43**, 1203.
- Sonnenblick, E. H., G. Glick, A. G. Morrow, and E. Braunwald. Force-velocity relations in the human heart (abstract). *J. clin. Invest.* 1964, **43**, 1245.
- Glick, G., E. H. Sonnenblick, J. F. Williams, Jr., and E. Braunwald. Effects of exercise performed at constant heart rate on myocardial force-velocity relations and ventricular dimensions in intact unanesthetized man (abstract). *Circulation* 1964, **30** (suppl. 3), 85.
- Glick, G., E. H. Sonnenblick, and E. Braunwald. Myocardial force-velocity relations studied in intact unanesthetized man. *J. clin. Invest.* 1965, **44**, 978.
- Sonnenblick, E. H. Series elastic and contractile elements in heart muscle. Changes in muscle length. *Amer. J. Physiol.* 1964, **207**, 1330.
- Chidsey, C. A., E. Braunwald, and A. G. Morrow. Catecholamine excretion and cardiac stores of norepinephrine in congestive heart failure. *Amer. J. Med.*, in press.
- Chidsey, C. A., G. A. Kaiser, E. H. Sonnenblick, J. F. Spann, and E. Braunwald. Cardiac norepinephrine stores in experimental heart failure in the dog. *J. clin. Invest.* 1964, **43**, 2386.
- Aygen, M. M., and E. Braunwald. Studies on Starling's law of the heart. VIII. Mechanical properties of human myocardium studied in vivo. *Circulation* 1962, **26**, 516.
- Ross, J., Jr., and E. Braunwald. The study of left ventricular function in man by increasing resistance to ventricular ejection with angiotensin. *Circulation* 1964, **29**, 739.
- Ross, J., Jr., and E. Braunwald. Studies on Starling's law of the heart IX: The effects of impeding venous return on performance of the normal and failing human left ventricle. *Circulation* 1964, **30**, 719.
- Mitchell, J. H., A. G. Wallace, and N. S. Skinner, Jr. Intrinsic effects of heart rate on left ventricular performance. *Amer. J. Physiol.* 1963, **205**, 41.
- Kruta, V., and P. Braveny. Différences physiologiques entre le myocarde du rat et de certains autres mammifères. *J. Physiol. (Paris)* 1960, **52**, 137.
- Hajdu, S., and E. Leonard. The cellular basis of cardiac glycoside action. *Pharmacol. Rev.* 1959, **11**, 173.

26. Koch-Weser, J., and J. R. Blinks. The influence of the interval between beats on myocardial contractility. *Pharmacol. Rev.* 1963, **15**, 601.
27. Bowditch, H. P. Über die Eigenthümlichkeiten der Reizbarkeit, welche die Muskelfasern des Herzens zeigen. *Ber. sächs. ges. (Akad.) Wiss.* 1871, 652.
28. Braunwald, E., S. J. Sarnoff, and W. N. Stainsby. Determinants of duration and mean rate of ventricular ejection. *Circulat. Res.* 1958, **6**, 319.
29. Ross, J., Jr., J. W. Linhart, and E. Braunwald. Effects of altering heart rate by electrical stimulation of the right atrium in man: studies at rest, during muscular exercise, and isoproterenol infusion. *Circulation*, in press.
30. Britman, N. A., and H. J. Levine. Contractile element work: a major determinant of myocardial oxygen consumption. *J. clin. Invest.* 1964, **43**, 1397.