

Force-velocity relations in mammalian heart muscle

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SONNENBLICK, EDMUND H. *Force-velocity relations in mammalian heart muscle*. Am. J. Physiol. 202(5): 931-939. 1962.— Force-velocity relations were studied in the cat papillary muscle. As with skeletal muscle, a characteristic relation has been demonstrated between the velocity of shortening (V) and the force developed (P_0). Two generalities have been shown to pertain. First, increasing initial muscle length increases the maximal developed force (P_0) without a change in the maximal velocity of shortening (V_{max}). Secondly, at any one muscle length, changes in frequency of contraction and chemical environment (increased calcium and norepinephrine) increase V_{max} with a variable change in P_0 . Changes in V_{max} thus help to characterize an inotropic intervention (altered contractility). Work and power, at any one muscle length, are functions of afterload, with maxima when the load is approximately 40% of isometric tension. With increasing initial muscle length, the work and power at any one afterload as well as the maximal work and power of the muscle are both increased. At constant initial length, positive inotropic interventions (increased frequency, increased calcium, and norepinephrine) increase the work at any one afterload as well as shift the maximal work potential to a higher afterload. Work performance thus depends on muscle length, the prevailing force-velocity curve, and the afterload at which the muscle is operating.

THE ALTERED DYNAMICS that can be induced in the heart by various interventions have been the subject of widespread investigation from which much useful information has been obtained. In such preparations, however, the ability to acquire data for the analysis of heart muscle mechanics on a level comparable to that available for skeletal muscle (1-6) is limited by the relatively complicated geometry of the heart and the consequent difficulty of making certain measurements. The use of isolated papillary muscle, even though possibly introducing other limitations, appreciably diminishes those present when examining the intact heart.

The experiments described in this communication were designed with three objectives. The first was to differentiate, if possible, between the altered dynamics resulting from increasing fiber length and those resulting

from changes in contractility or inotropism, e.g. an altered contraction from the same initial fiber length in heart muscle. The second was to acquire data on the basis of which certain of the similarities and differences between cardiac and skeletal muscle could be more concisely described. The third was to obtain and analyze the data so as to relate them in a meaningful manner to information already available on the intact heart.

The relation between the velocity of isotonic shortening (V) and the force developed (P), the force-velocity relation, has been termed the most fundamental mechanical property of the contractile portion of the muscle during activity (1, 2, 4) and has been shown to apply to widely divergent varieties of smooth (7, 8) and striated muscle (1, 2, 5, 9-11).

In skeletal muscle, at any one muscle length and temperature, the force-velocity relation is unique, such that the maximal velocity of shortening, i.e., the velocity of shortening the muscle would achieve if carrying no load (V_{max}), and the maximal force the muscle can develop (P_0) are constant (5, 12). On the other hand, in heart muscle it would appear that the force-velocity relation is not constant for, as Abbott and Mommaerts (13) have shown, this relation may be significantly altered by changes in the frequency of contraction and extrasystolic potentiation.

Evidence will be presented in support of the view that, in cardiac muscle, two important generalities obtain. The first is that the increased force of contraction (P_0), observed with increasing initial muscle length, occurs without alteration of V_{max} . In contrast, whenever at any given muscle length an inotropic effect is induced (altered contractility), this is accompanied by a change in V_{max} . This latter generality applies whether the inotropic effect results from a change in the frequency of contraction or an alteration of the chemical environment.

A brief report of this material has been presented elsewhere (14).

METHODS

Cat papillary muscle. Papillary muscles were obtained from the right ventricles of cats (0.5-1.5 kg), anesthetized with intraperitoneal sodium pentobarbital (25

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mg/kg). Individual muscles were 7.0–13.0 mm in length with a cross-sectional area (calculated on the basis of weight, assuming the muscle to be a cylinder) of 0.7–1.50 mm². Long thin preparations were selected, since these were found to be most stable. Thicker preparations (more than 1.0 mm²) appeared to deteriorate with time, possibly secondary to the limits of oxygen diffusion (15). With precautions as to thickness of

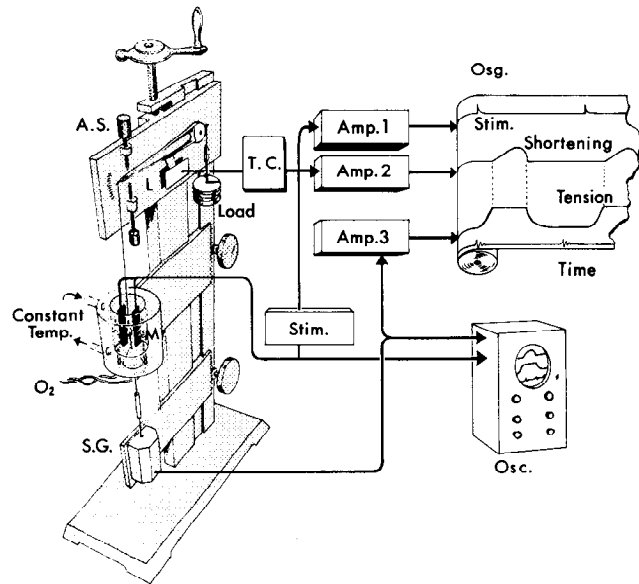


FIG. 1. Diagram of apparatus allowing for simultaneous recording of tension and isotonic shortening. M = papillary muscle; S.G. = strain gauge tension transducer, L = isotonic lever; A.S. = stops for lever; T.C. = tuned circuit for lever.

preparations and rapidity of dissection, papillary muscles were obtained which were stable for at least 12 hr. Following the minimal exposure to air involved in removal of the heart from the animal, the papillary muscle was placed in a Lucite chamber and bathed in a bicarbonate buffered Krebs-Ringer solution (Na⁺ 148 mEq, K⁺ 4.0 mEq, Ca⁺⁺ 5.0 mEq, Mg⁺⁺ 2.5 mEq, Cl⁻ 128 mEq, HCO₃ 25 mEq, HPO₄⁻ 1.2 mM, and glucose 5.6 mM/liter). When bubbled with 95% O₂ and 5% CO₂, the bath pH was 7.4. Bath temperature was maintained constant during any particular series of experiments, using a Haake controlled temperature circulating pump (Brinkman Instruments, Inc., N.Y.). Most experiments were performed at 21–23 C, while some were performed at 35–10 C, as desired.

Simultaneous length and tension measurement. A simplified diagram of the apparatus employed is provided in Fig. 1. The lower end of the papillary muscle (M) was tied to a fine stainless steel needle. This needle passed through a close tolerance aperture at the base of the bath, then via an insulating low compliance connection to a tension transducer (S.G.). The mass of the needle was balanced by a light silver wire spring. The tension transducer (Statham model G1-1-1000) had a linear output over the range of 0–30 g, well within the range of the forces encountered in these experiments. The displacement of the transducer was less than 10μ for 5 g load, ensuring isometric measurements when desired, as well as minimal inertia from this component of the system.

The tendinous upper end of the papillary muscle was tied by noncapillary silk thread to a wire connected to a low inertia, rigid isotonic lever (L) (designed by M. O.

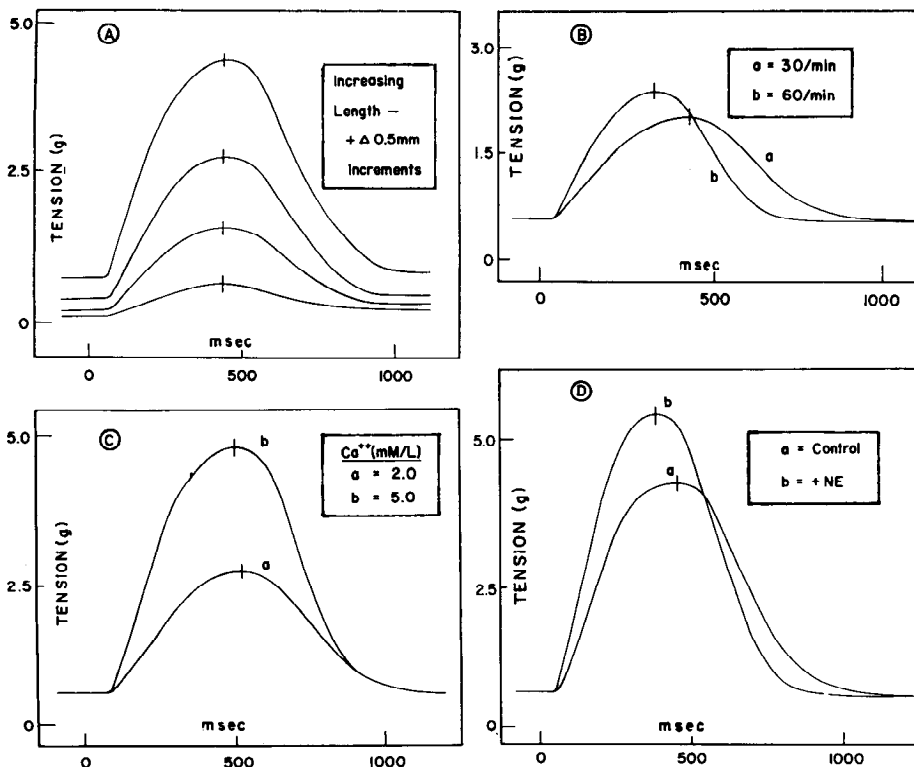
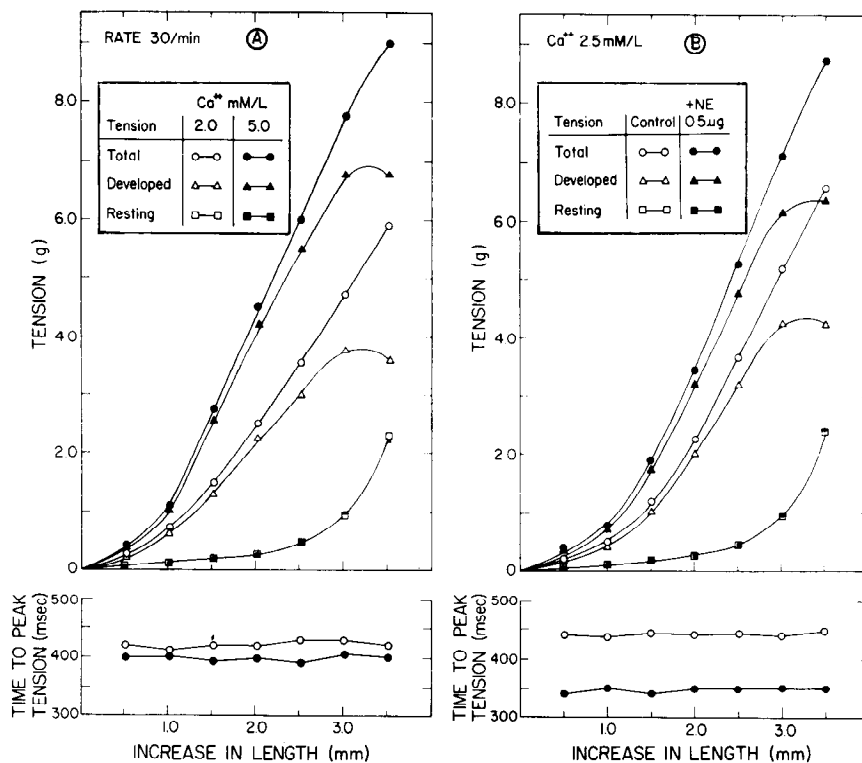


FIG. 2. Superimposed isometric contractions. Temperature 23 C. Frequency 30/min. Ordinate: isometric tension; abscissa: time after stimulation. A: Increasing initial muscle length. Increments of 0.5 mm; initial muscle length 8.5 mm. B: Increasing frequency of stimulation from 30 to 60/min. C: Increasing [Ca⁺⁺]_o from 2.0 to 5.0 mM/liter. Frequency 30/min. D: Effect of adding norepinephrine (0.05 μg/ml). Frequency 30/min. [Ca⁺⁺]_o 2.5 mM/liter.

FIG. 3. Length-tension diagrams. *A*: Increasing $[Ca^{++}]_0$ from 2.0 to 5.0 mM/liter; *B*: Addition of norepinephrine, 0.05 μ g/ml. Temperature 25 C. Initial muscle length 10.5 mm. Cross section 1.20 mm². Frequency 30/min. Ordinate: upper panels—tension; lower panels—time from onset of contraction to peak isometric tension. \circ — \circ control, \bullet — \bullet postintervention. Total tension equals resting tension plus developed (or active) tension. Abscissa: increase in muscle length in mm.



Schilling, University of California, Los Angeles) (16). The lever was designed with a 25:1 lever arm ratio with a moment of inertia of 15 g-cm² around the center of rotation, providing an equivalent mass of less than 300 mg (16). For isotonic studies, the afterload was attached to the isotonic lever via an extensible segment of rubber, to further minimize inertia. A light vane attached to the lever arm provided one plate of a variable capacitance activated by a tuned circuit (T.C.), the electrical output of which was linear over a displacement of 2.0 cm and sensitive to approximately 0.5 μ . Maximal rise time for linear recording was approximately 1000 cm/sec. Since maximal muscle displacements were only 1.5 cm/sec, the frequency response of the system was quite adequate. Adjustable stops (AS) allowed fixation of the initial muscle length for isotonic studies as well as complete fixation of the lever for isometric studies.

Stimulation of the muscle was provided by a Grass impulse stimulator (model S₄C). Two platinum electrodes (0.5 X 2.0 cm) were used along the parallel aspect of the muscle to provide transverse field stimulation. A supramaximal square wave stimulus was employed (generally 15 v for 1.0 msec) which produced a consistent all-or-none response.

Tension development and linear displacement were recorded simultaneously along with a stimulation artifact and time marker on a dual-trace oscilloscope (Osc) and a multichannel direct-writing Sanborn oscillograph (Osg). For good resolution, recordings were generally made at a paper speed of 100 mm/sec. During isotonic measurements, initial velocity of shortening was calculated from the slope of the initial course of shortening.

TABLE 1. Active stiffness (dp/dl) of papillary muscle

A. Changing frequency. Preload 0.2 g; afterload 0.8 g; Lo 9.5 mm; temp. 22 C; cross section 0.8 mm²

Rate per min	dl/dt,* mm/sec	dp/dt,† g/sec	dp/dl,‡ g/mm	Latency,§ msec
6	1.24	4.56	3.68	45
20	2.50	9.02	3.63	40
30	3.04	10.9	3.60	30
60	4.60	16.8	3.65	22
90	4.63	17.6	3.69	20
120	4.56	17.5	3.83	18

B. Increasing calcium and norepinephrine. Preload 0.2 g; afterload 1.0 g; Lo 9 mm; temp 21 C; cross section 0.7 mm²

Rate per min	Ca ⁺⁺ , mm/sec	dl/dt	dp/dt	dp/dl	Latency
30	2.5	1.22	4.85	3.97	40
60	2.5	2.95	12.0	4.02	30
60	2.5 + NE (.05 μ g) (wash)	6.10	24.8	4.07	22
60	2.5	3.75	14.7	3.97	30
60	5.0	5.10	20.1	3.96	25
60	5.0 + NE (0.5 μ g)	7.95	31.1	3.94	18

Constant load (preload plus afterload) records have been taken from sequential force-velocity relation curves. Frequency, calcium, and norepinephrine have been changed as noted. Note that dp/dl is not changed by the described interventions.

* dl/dt = initial velocity of isotonic shortening at given load.

† dp/dt = rate of force development at given load.

‡ dp/dl or active stiffness ($\frac{\Delta \text{tension}}{\Delta \text{length}}$) at given load = $\frac{dp/dt}{dl/dt}$.

§ Time from stimulus to onset of force development.

The muscle chamber was affixed to a heavy base plate which was placed on vibration dampers. The isotonic lever was adjusted with a Palmer stand, while the tension transducer was attached to a Brinkman micrometer

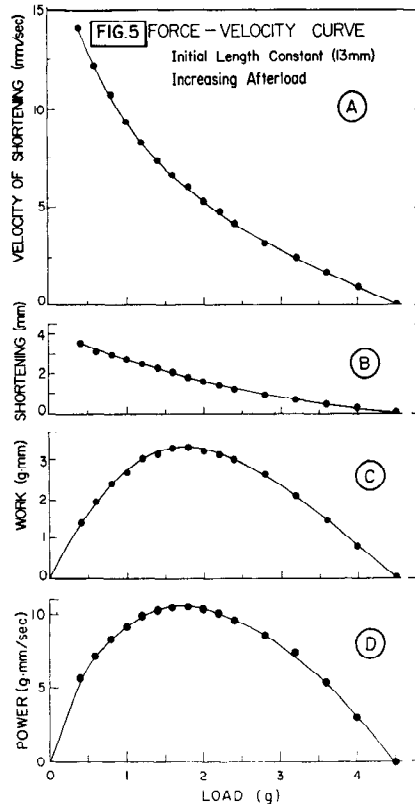
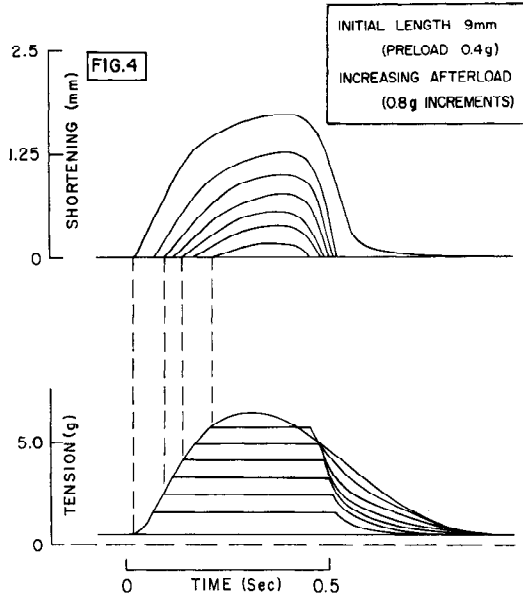


FIG. 4. Superimposed sequential tracings of isotonic shortening with increasing afterloads. Temperature 21 C. Frequency 30/min. Muscle length 9.5 mm. Cross section 1.15 mm². Initial length constant with preload 0.4 g. Ordinate: upper tracings—*isotonic shortening*; lower tracings—*tension development*. Abscissa: *time after stimulation*.

FIG. 5. The force-velocity relation, work and power. Temperature 21 C. Rate 30/min. Muscle length 13.0 mm; cross section 1.25 mm. Ordinate: A: *initial velocity of isotonic shortening*; B: *extent of shortening*; C: *work (shortening × load)*; D: *power (load × velocity)*. Abscissa: *load (preload 0.4 g + afterload)*.

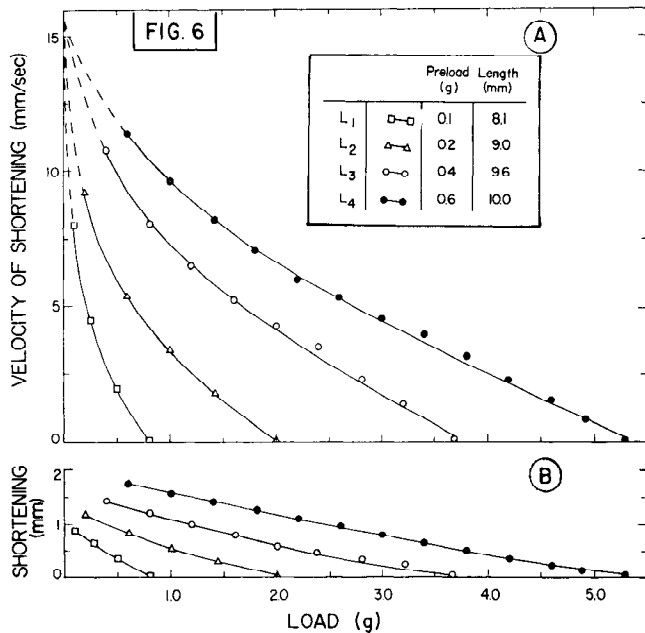
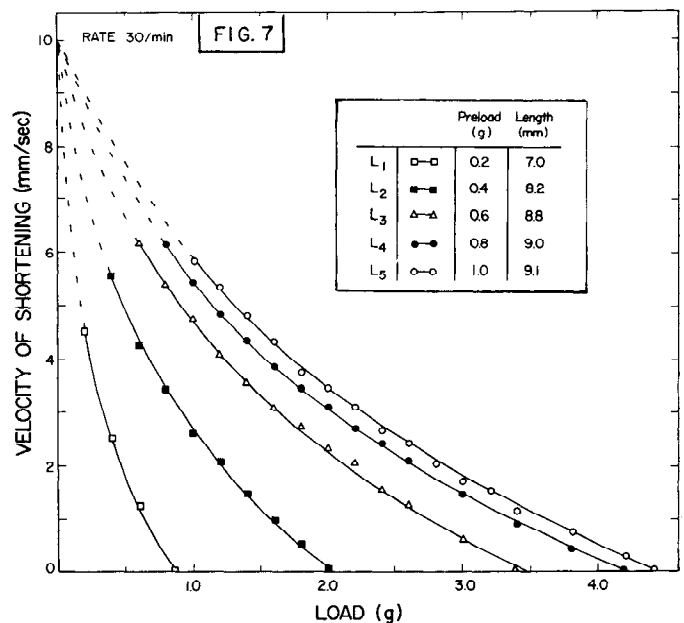


FIG. 6. Force-velocity relations with increasing initial muscle length. Temperature 21.5 C. Rate 30/min. Muscle length 8.1 mm; cross section 1.20 mm². Ordinate: A—*initial velocity of isotonic shortening*; B—*extent of shortening*. Abscissa: *total load in g (preload + afterload)*. Muscle length increased by increasing



preload (L₁ to L₄). Velocity of shortening has been extrapolated to zero load in order to approximate V_{max} (dotted lines).

FIG. 7. Effect of large preloads on the force-velocity relation. Temperature 23.5 C. Rate 30/min. Initial length 7.0 mm. Cross section 1.35 mm². Ordinate: *velocity of shortening*. Abscissa: *load*. Initial length increased by increasing reloads (L₁ to L₅).

stage. Both tension transducer and isotonic lever stages were fixed to the same plate as the muscle bath. The data presented below represent the results of the analysis of 51 technically satisfactory preparations out of an attempted 79.

RESULTS

Isometric Contraction and Length-Tension Relations

Effect of inotropic interventions on isometric contraction. When the isotonic lever was fixed and external shortening

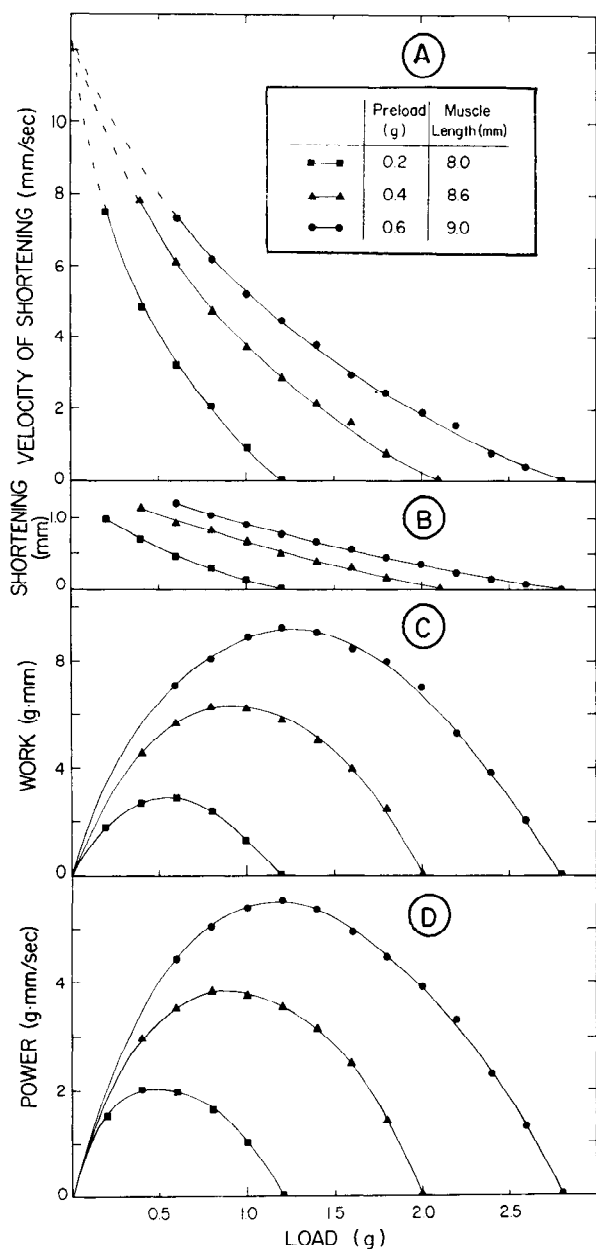


FIG. 8. Effect of increasing initial length on work and power. Initial length 8 mm. Cross section 1.25 mm^2 . Rate 30/min. Temperature 23°C . Ordinate: A—velocity of shortening; B—shortening; C work (shortening \times load); D—power (velocity \times load). Abscissa: load.

of the muscle thus prevented, isometric tension was recorded. In Fig. 2 are shown representative superimposed isometric contractions from a single experiment in which four separate types of intervention were made. In panel A, initial length of the muscle was increased. This increased the rate of tension development and the developed tension. However, the time from onset of contraction to peak developed tension was not changed by increasing fiber length as long as frequency of contraction, temperature, and chemical environment were kept constant. In Fig. 2B the effect of increasing frequency of contraction is presented. Both the rate of

tension development and the developed tension increased. This was, in addition, accompanied by a significant shortening in the time to peak tension. When $[\text{Ca}^{++}]_0$ was increased (Fig. 2C), the rate of tension development and the developed tension were increased, while the time to peak tension was only slightly shortened. When norepinephrine was added to the bath (Fig. 2D), along with an increase in the rate of development of tension and developed tension, there was a substantial shortening in the time to peak tension. An observation of interest was that the level of $[\text{Ca}^{++}]_0$ appreciably modified the characteristic response of the muscle to norepinephrine. At both high (7.5 mM/liter) and low (1.0 mM/liter) $[\text{Ca}^{++}]_0$, norepinephrine induced a substantial shortening of the time from the onset of contraction to peak tension. However, when $[\text{Ca}^{++}]_0$ was low, the relative increase in the peak tension developed was greater than when $[\text{Ca}^{++}]_0$ was high.

Length-tension relations. Experiments in which initial muscle length was increased while recording tension, both at rest and during contraction, allowed a full description of the length-tension relation of the muscle to be made. A representative example of this is shown in Fig. 3. Contractions were studied above that point (L_0) where both resting and developed tension were at or near zero. As initial muscle length was increased, resting tension and developed tension increased. Resting tension rose slowly until approximately a 25–30% increase in length above L_0 was attained. At this point, a steeper rise in resting tension occurred. Only above this point was significant stress relaxation seen (17, 18). Since it was observed empirically that maintained high resting tension produced extensive stress relaxation and damage to the preparation, excessive or prolonged extension of the muscle was avoided.

No change in extensibility was observed when the developed isometric tension was increased due either to increasing $[\text{Ca}^{++}]_0$ or adding norepinephrine. As is shown in Fig. 3, increasing the length did not change the time from onset of contraction to peak tension. When $[\text{Ca}^{++}]_0$ was increased, time to peak tension was only slightly shortened but then remained constant over the range of muscle lengths examined. With the addition of norepinephrine, time to peak tension was more markedly shortened and, again, this remained constant over the entire range of muscle lengths studied.

Latency. The time interval from stimulation to the onset of force development (latency) was 30–40 msec at $22\text{--}24^\circ \text{C}$ with a stimulation frequency of 30/min, and was not significantly changed by increasing muscle length. However, with increasing frequency of contraction, a shortening of latency was noted. At a frequency of 1 contraction/min (22°C), latency was 50–55 msec; at 120/min, latency was shortened to 25–30 msec. Both the addition of norepinephrine and increasing calcium produced a shortening of latency of variable degree, at times by as much as 50% of its initial value (see Table 1). It should be noted, however, that present studies did not allow accurate quantitation of small latency changes of less than 5 msec.

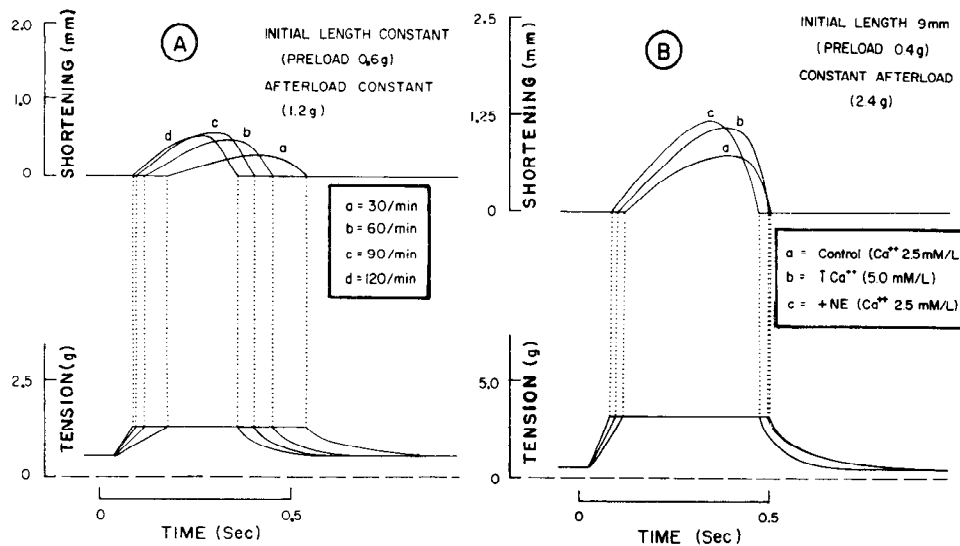


FIG. 9. Inotropic interventions and isotonic shortening with constant initial length, and load. Superimposed tracings. Ordinate: upper—shortening; lower—force development. Abscissa: time after stimulation. *A*: increasing frequency of contraction. Initial length 9.5 mm with preload 0.6 g. Cross section 1.15 mm², temperature 23 C. Rate increased progressively from 30 to 120 contractions/min (a to d). *B*: increasing $[Ca^{++}]_o$ and norepinephrine. Initial length 9 mm with preload 0.4 g. Cross section 1.35 mm². Temperature 23 C. Rate 30/min. In both sets of experiments the velocity of shortening (dl/dt) and the rate of tension development (dp/dt) are increased proportionally.

Isotonic Shortening and Force-Velocity Relations

Force-velocity relation with constant initial length. When the muscle was allowed to contract isotonicly, its initial length was set by a small load on the muscle prior to contraction, i.e., the preload. The lever stop (A.S.) was then adjusted so that subsequently increasing the load would not produce any change in initial length. The total load minus the preload constituted the afterload, since this load was not sensed until after the onset of contraction. The plot of the force developed (P) (which in the afterloaded condition equals the total load) and the initial velocity of isotonic shortening (V) is a curve, describing the force-velocity relation (2,6).

In Fig. 4, superimposed segments of sequential tracings of isotonic shortening with increasing afterloads are illustrated. Initial length was determined by a preload of 0.4 g and held constant. As the afterload was increased, the muscle developed increased force to meet this load, following which shortening began. The course of isotonic shortening with increasing afterloads is shown in the upper tracings of Fig. 4. As afterload was increased, the initial velocity of isotonic shortening and the extent of shortening progressively decreased.

Theoretically, with no load on the muscle, the velocity of shortening is maximal (V_{max}). Experimentally, the closest one can approach such a condition with heart muscle is to use the smallest preload from which a contraction occurs that produces analyzable data. Since, in accordance with the resting length-tension relation of the papillary muscle, a significant preload is necessary to establish the initial length that will produce such a contraction, V_{max} cannot be determined directly but may be estimated by extrapolation of the force-velocity curve to zero load. When the afterload is increased to where no apparent muscle shortening occurs, the isometric twitch tension is recorded (P_o). The connotation of P_o as used here should be noted since, as it is generally employed in describing skeletal muscle (2), it refers to the tetanic isometric tension.

In Fig. 5, the initial velocity of isotonic shortening,

work (load times shortening), and power (load times velocity) are plotted against load, which was varied by varying afterload. As load was increased, a characteristic relation was noted between velocity of shortening and load (Fig. 5A). With increasing load, velocity of shortening (Fig. 5A) and shortening (Fig. 5B) progressively decreased. Work, on the other hand (Fig. 5C) increased with increasing load, reaching a maximum at a load approximately 40% of isometric tension. With further increases in afterload, work declined, reaching zero when the load was too large to allow shortening. In such experiments, work has been calculated using total load. Subtraction of the preload from the total load, in calculating work, as suggested by Buchthal *et al.* (11), reduced total work but yielded a qualitatively similar curve. However, calculation of work using total load was used since once shortening has begun, the preload as well as the afterload must be moved by the contractile element and hence should be considered for work calculation. Power (load times velocity) was also noted to be dependent on the load in a similar manner to work (Fig. 5D).

Effect of varying initial length on force-velocity relation. The effect of increasing initial length on the force-velocity relation of the muscle is illustrated in Fig. 6, in which initial length was increased by increasing the preload in a stepwise manner. With each increase in initial length, a new curve was obtained yielding a series of force-velocity curves which, when extrapolated to zero load, produced a general convergence to a common V_{max} (Fig. 6A and Fig. 7). This convergence was observed in all twelve such experiments.

Figure 7 shows a family of force-velocity curves demonstrating that, as would be expected from the resting length-tension relation, the shift to the right of the force-velocity curve diminishes at the higher preloads, since a smaller increment in initial length occurs for any given preload increase in that range.

Effect of varying initial length on relations between load, work, and power. At any given initial length, with con-

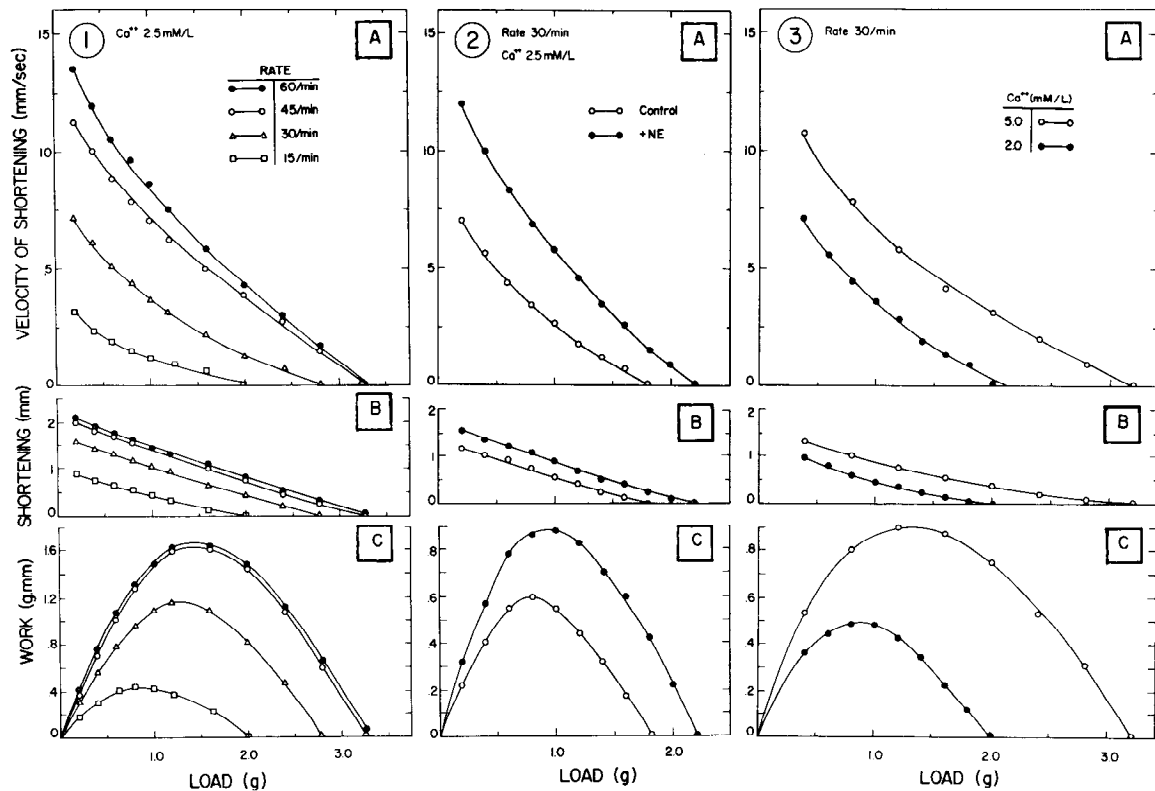


FIG. 10. Effect of inotropic interventions on the force-velocity relation. Ordinate: A—velocity of shortening; B—shortening; C—work. Abscissa: load. Panel A: Increasing frequency. Temperature 22 C. Initial length 10.5 mm. Cross section 1.3 mm². Frequency increased from 15 to 60/min. Panel B: Addition of

epinephrine (0.05 μ/ml). Temperature 21 C. Initial length 10 mm. Cross section, 1.4 mm². Panel C: Increase of $[Ca^{++}]_0$ from 2.0 to 5.0 mM/liter. Temperature 20 C. Initial length 8 mm. Cross section 1.25 mm².

stant frequency and chemical background, the work and power of the muscle were necessary functions of the load (Fig. 5C, D). As initial muscle length was increased (Fig. 8), the maximal work the muscle could perform as well as the load at which this maximal work was performed, were both increased. At any one load, increasing initial muscle length increased the work accomplished and, by increasing the velocity of shortening at that load, increased the power of the muscle as well (Fig. 8D).

Effect of inotropic interventions on force-velocity relation. When preload, initial length, and afterload were held constant, the rate of tension development (dp/dt) and the velocity of shortening (v or dl/dt) could be changed by varying the frequency of contraction (Fig. 9A), increasing $[Ca^{++}]_0$ (Fig. 9B), or the addition of norepinephrine (Fig. 9B). If, during activity, changes in the elastic compliances of the muscle were not changed by the inotropic intervention, it would be anticipated that a constant relation would remain between the velocity of shortening and the rate of force development at any one afterload.¹ As in Fig. 9 and Table 1, this was

¹ At any one afterload, the active modulus of elasticity (dp/dl) can be calculated, since $dp/dt = dp/dl \times dl/dt$, where dp/dt = the rate of force development and dl/dt = the velocity of shortening. Hence, $dp/dl = \left(\frac{dp/dt}{dl/dt} \right)$ (2, 3). The term "active stiffness" has been used instead of modulus of elasticity since normalization for cross section and length has not been employed.

generally observed, suggesting that an inotropic intervention does not produce its effect by alteration of the characteristics of elastic components.

The effects of various inotropic interventions on the force-velocity relation are illustrated in Fig. 10. In each experiment the initial muscle length was held constant throughout. In panel 1A, it can be seen that as frequency of contraction was increased there was an increase in V_{max} . At lower frequencies there was also an increase in P_0 , but, as frequency was further increased, V_{max} increased with little or no increase in P_0 . Further, with increasing frequency, shortening and hence work increased at any one afterload. However, with continued increases in rate, a point was reached where, despite further increases in the velocity of shortening, an increase in shortening and thus work were not seen. From Fig. 9A it can even be seen that a decrease in shortening may actually occur at high frequencies and hence a decrease in calculated work may actually be observed, despite a continued increase in V_{max} . At higher frequencies, however, the influence of inadequate relaxation and relative tissue hypoxia enters consideration.

When norepinephrine was added to the bath (Fig. 10, panel 2), an increase in both V_{max} and P_0 was observed. When $[Ca^{++}]_0$ was increased (Fig. 10, panel 3) there was also an increase in both V_{max} and P_0 , but, unlike the results obtained with norepinephrine and with increased frequency, there was generally a parallel shift of the

TABLE 2

	V_{max}	Po	Time to Peak Isometric Tension
Changing initial muscle length	NC*	↑↑	NC
Increasing frequency of contraction	↑↑	↑ or NC	↓↓
Norepinephrine	↑↑↑	↑	↓↓
Increasing calcium	↑↑	↑↑	↓

* NC = no change.

force-velocity curve. This difference in the qualitative nature of the shift of the force-velocity curve with norepinephrine compared to that of increased $[Ca^{++}]_0$ was experimentally quite consistent in 26 such experiments. Both norepinephrine and increased $[Ca^{++}]_0$ increased the extent of shortening (Fig. 10, 2B and 3B) and thus the work at any one afterload (Fig. 10, 2C and 3C). With all these interventions, the muscle was also more powerful at any load as velocity was increased. Further, norepinephrine and increased calcium increased the maximal work that the muscle could do and also increased the afterload at which this maximal work was performed.

In Table 2, these results are briefly summarized.

DISCUSSION

Force-velocity relations. Abundant evidence has been obtained in skeletal muscle for considering the fundamental unit of muscle as an active contractile element in series with a passive elastic component (2). According to Hill (4), the most fundamental property of the active contractile component is the characteristic hyperbolic relation between the velocity of shortening (V) and the developed force (P) (2). It is the readiness with which heart muscle can alter its force-velocity relations under the influence of changing frequency of contraction and altered chemical environment which allows for changing contractility of the myocardium and reveals a basic difference between heart and skeletal muscle.

Two important generalities can be made about heart muscle. The first is that an increase in muscle length induces an increase in the force of contraction (19–21). This generality also applies to skeletal muscle (22–23). In the present study, it has been demonstrated that with increasing fiber length the increase in force (P_0) is engendered without a change in V_{max} . V_{max} thus helps to define and quantify the basic state of cardiac muscle, i.e. its contractility. Whether or not this constancy of V_{max} with changing length also applies to skeletal muscle is as yet unclear (11, 24).

The second generality about heart muscle is that, at any one muscle length, increasing frequency of contraction or changing chemical environment may readily alter rate of force development as well as developed force without prolongation of contraction (25). Further, these inotropic interventions are marked by a change in V_{max} , as Abbott and Mommaerts (13) have suggested for an increase in frequency of contraction and extra-

systolic potentiation, and the present study has demonstrated with an altered chemical environment. In changing V_{max} , an inotropic intervention induces a change in the basic state of the muscle and thus an altered state of contractility is engendered. The ready ability of heart muscle to alter V_{max} forms a basic difference from skeletal muscle where V_{max} (except with changing temperature) is constant under physiological conditions (2, 5, 12).

Since the length-tension relation of the series elastic element of heart muscle is nonlinear (13), the form of the isometric twitch will be a complex function of the force-velocity relation, the compliances of the muscle, and the duration of full activity of the muscle (3). From the observations of the constancy of the active modulus of elasticity (active stiffness) of heart muscle at any one length and load, it would appear most unlikely that changes in elastic compliances participate in inotropic changes. It should be further noted that twitch potentiation might result from prolongation of the duration of contraction with an unchanged rate of force development (dp/dt), such as has been observed with skeletal muscle (5, 24). However, in mammalian heart muscle, prolongation of twitch duration or the duration of contractile activity is not observed with physiological inotropic interventions (14). On the contrary, inotropic interventions are generally accompanied by some shortening of the duration of contraction. Thus, changes in the rate of force development at any one muscle length should be a function of changes in the force-velocity relation alone, provided that changes in the synchronicity with which the contractile elements are activated does not take place (26).

A potential limitation arises when the force-velocity equation of Hill (2), which was originally formulated for skeletal muscle in terms of tetanus tension, is applied to the twitch, since heart muscle cannot be tetanized (19). In the skeletal twitch, isometric tension falls short of tetanus tension due to a limitation of activation time (4). It is probable that this also occurs in the heart muscle twitch, but the extent to which the twitch approaches a theoretical tetanus tension is not known. However, the use of reduced temperatures (20–23 C), which prolong the duration of activation of the muscle with only a small decrease in the rate of tension development (14), may allow the twitch to approach tetanic tension. Further, an inability to attain P_0 with any assurance makes calculation of the constants a and b for the Hill equation somewhat hazardous. Nevertheless, a good measure of V_{max} can be attained and a reasonable estimation of the entire force-velocity curve empirically made.

Theoretical considerations. Some theoretical implications of alterations of the force-velocity relation are of interest. It has been postulated by Podolsky (27) that V_{max} may be considered as an experimental measure of the absolute rate of the force generating process of the muscle, while P_0 is a function of the number of active tension-generating contractile sites. Podolsky has further theorized that a fixed amount of an activating substance per contractile unit may be released with the onset of activation and

consumed at a rate dependent on V_{\max} (27). When this substance is consumed, relaxation ensues.

Thus, increasing muscle length which increases P_0 without a change in V_{\max} may be the result of making more qualitatively similar contractile sites available for interaction without changing the rate of this interaction. The constancy of V_{\max} with changing muscle length is consonant with the view that no change in the absolute rate of force generating processes of the muscle has occurred. Further support for the constancy of V_{\max} is found in the lack of change in the time to peak isometric tension or the duration of contractile activity (14). This view would also be in accord with Huxley's theoretical model of the contractile process (28).

In contrast, an increase in V_{\max} accompanies an inotropic intervention. An inotropic intervention, whether increased frequency or an altered chemical environment, thus implies an acceleration of the rate determining process of the muscle (27). An accompanying change in P_0 , whether induced by activation of more contractile sites or a further activation of the same units, helps to define the form of this inotropic intervention.

The underlying phenomena that allow for this change in the rate of mechanochemistry of the muscle are a matter of speculation. It would appear, however, that membrane phenomena, which somehow couple excitation and mechanical response, mediate both the rate of mechanochemistry and the duration of activity (16).

It should be noted that in skeletal muscle, adrenaline may also increase twitch tension. However, this results from prolongation of the duration of contraction or the active state without a change in tetanic tension (P_0) or an alteration of the force-velocity relations of the muscle (29). Similarly, when calcium is altered over wide ranges, skeletal contraction is unaltered (30). It is thus evident that skeletal muscle may modulate force by the duration of contraction but, unlike heart

muscle, does not have the ability to modulate its intrinsic velocity (V_{\max}).

Work, power, and the intact heart. Work and power are necessary functions of afterload in accordance with the force velocity relation of the muscle. It is known from skeletal muscle (31) and affirmed for heart muscle (32, 33) that the work a muscle can do at any one length is a function of the load it carries. However, unlike skeletal muscle, heart muscle may alter work and power at any one load and muscle length by nature of its shifting force-velocity curves under varying frequency and chemical environment. For maximal work to be produced, the load must be concomitantly increased. Work per contraction is thus a complex function of initial muscle length, load, and the force-velocity curve on which the muscle is operating. By analogy, in the intact heart these parameters would correlate with ventricular filling pressure (LVED), ejection resistance (aortic pressure), and the inotropic state of the myocardium. In this lies the basis of the ventricular function curve as a measure of "contractility" in the intact ventricle (34).

An evaluation of the basic state of the intact myocardium is also possible from the knowledge that, at any one muscle length, the rate of tension development (dp/dt) is a function of the force-velocity relation. Since the duration of activity of the muscle is not altered by increasing length (14), the ratio of dp/dt to the integrated developed isometric force (IIT) should be constant for any one state of contractility, independent of muscle length. Such has been shown to obtain in the intact heart (35).

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