A STUDY OF INOTROPIC MECHANISMS IN THE PAPILLARY MUSCLE PREPARATION*

By B. C. ABBOTT AND W. F. H. M. MOMMAERTS‡

(From The Department of Zoology and Medicine (Los Angeles County Heart Association Cardiovascular Research Laboratory), The University of California at Los Angeles)

(Received for publication, August 25, 1958)

ABSTRACT

The length-tension diagram, the force-velocity relation, the characteristics of the series elasticity, and the duration of the active state have been studied on the papillary muscle preparation of the cat heart, and on other examples of cardiac muscle.

Positive inotropic changes such as the staircase phenomenon and post-extrasystolic potentiation occur without lengthening, but frequently with shortening, of the duration of the active state. They are accompanied by an increased velocity of contraction, and may be caused either by an intensification of the active state or by an alteration of the force-velocity characteristics of the contractile component.

The changes in the force-velocity relation point to an adaptation of the velocity-efficiency relation in dependence on the frequency of contraction.

INTRODUCTION

Certain of the basic mechanical properties of contractile tissues, which have been currently investigated for skeletal muscle (*e.g.* Hill, 1950; Wilkie, 1954, 1956 *a*), seem to be insufficiently known for the myocardium. Their understanding is necessary as the basis for the appreciation of cardiac dynamics, particularly in order to formulate, in fundamental terms, the variations in contractile strength encountered physiologically and pathologically, and the mechanisms with which these are accomplished.

The investigations reported in this paper, which were performed on papillary muscle preparations of mammalian hearts, were aimed primarily at an explanation of the staircase phenomenon and of post-extrasystolic potentiation, as examples of alterations of the contractile response. In the course of this work, observations were made on such features as the length-tension diagram, the force-velocity relation, the series elastic component, and the duration of the active state, most of which properties do not seem to have been investigated in

* This study was supported by grants from the National Heart Institute of the National Institutes of Health, and from the American Heart Association.

‡ Established Investigator of the American Heart Association, Departments of Medicine and Physiology, University of California at Los Angeles.

cardiac physiology. It appears from these results that the inotropic changes studied are operative by basically altering the force-velocity relation of the muscle, with or without concomitant changes in the intensity of the active state. These same dynamic changes also indicate that the velocity for optimal efficiency of the heart may be adapted to its frequency.

Methods

The Papillary Muscle.—Papillary muscle (Cattell and Gold, 1941) and frequently also trabeculae carneae (Ullrich and Whitehorn, 1956) preparations were obtained from the right ventricles of cats, and occasionally from rabbits, under ether anesthesia and artificial respiration with the usual precautions.[1] Temporary anoxia during or after the preparation was avoided by keeping the tissue in close contact with a fine stream of oxygen containing 2 per cent CO_2 throughout the dissection. The composition of the bathing solution was 161 mM NaCl; 5.6 mM $CaCl_2$; 5.6 mM KCl; 7.1 mM $NaHCO_3$; 5.6 mM glucose (Feigen *et al.*, 1952). Most experiments were done at 25°C. with scattered observations at other temperatures. Under these circumstances, with occasional changes of bathing solution, the preparations often survived as long as 2 or 3 days, without showing a marked decline in contractile strength notwithstanding prolonged experimentation. Spontaneous activity, which we tend to regard as a sign of partial anoxia under these conditions, was not as a rule observed except occasionally in an entirely fresh sample. Since the "resting length" of the muscle is not as definitive as it is in skeletal muscle, the preparation was usually held at a length at which resting tension began to be obvious, of the order of 0.25 gm., unless the nature of the experiment determined otherwise. The muscles were measured at this length, and weighed at the end of the experiment; usually, their cross-section as calculated from length and weight was about 2 $mm.^2$, with a length of 10 to 15 mm.

Stimulation (Fig. 1).—The muscle was mounted in a double walled lucite chamber, the peripheral space of which was perfused with water from a thermostat bath. The tissue was bathed in 5 ml. of medium through which the O_2–CO_2 mixture was bubbled continuously along two sides of the muscle from two openings in the bottom. Two opposite vertical walls consisted of sheet platinum electrodes, so that the muscles were stimulated between massive electrodes (*e*) similar to the design of Mostofsky and Sandow (1951). We are aware of the many problems involved in the geometry of electrode stimulation (*e.g.* Rushton, 1930) and state only that our method gave rise to all-or-none responses with sharply defined thresholds.

The stimulator for high current output, based upon the use of tektronix pulse and wave form generators, was designed and built by Mr. Edward Burkart.[2] Among its major features it can be mentioned that the polarity of the electrodes was reversed at each stimulation to preclude polarization phenomena. Notwithstanding the all-or-none character of the responses with regard to variation of the stimulus intensity, it was often observed that a small dissymmetry occurred in the response to each of

[1] Many of the preparations were given to us by Dr. William J. Whalen and Mr. Charles Dubkin of the Department of Physiology.

[2] The experimental devices designed by M. O. Schilling and E. Burkart will be described separately.

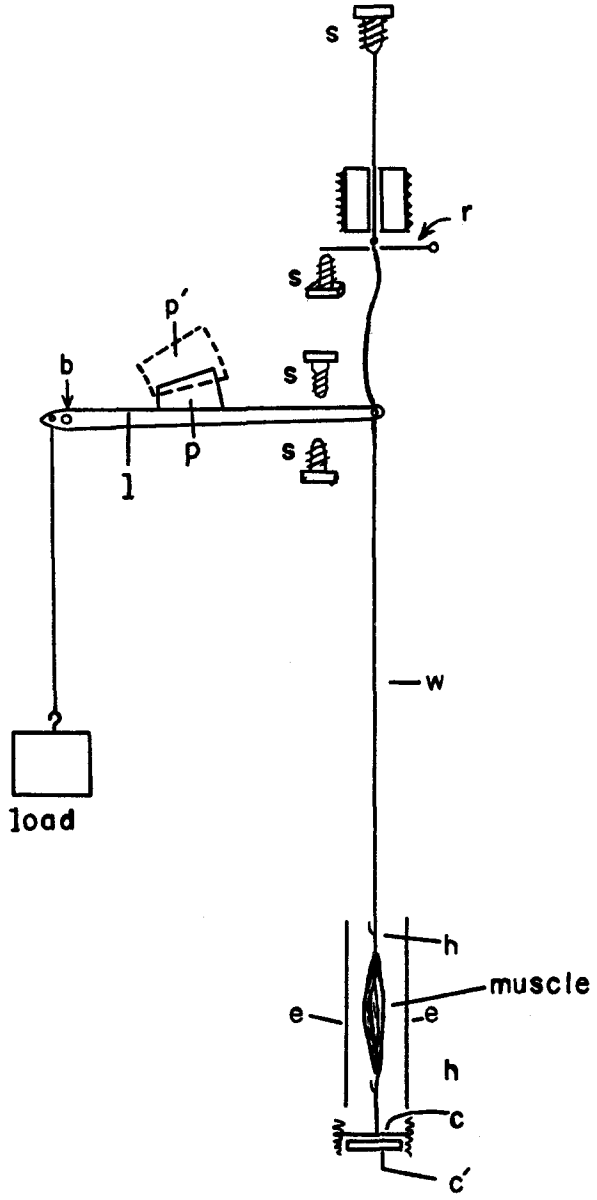

FIG. 1. Diagram of apparatus for the measurement of isotonic and isometric contractions, and of quick-release phenomena. Explanation of symbols in the text; s = adjustable stops.

the two polarities. When this happened, all crucial observations were done at the same polarity configuration. The stimuli consisted of rectangular pulses, mostly of 0.1 msec. duration. The stimulator contained a programming device by which selected complex patterns of stimulation could be performed automatically.

Recording of Tension.—For mounting, the muscle was tied at both ends to stainless steel hooks (*h*); at the apex, the shortest possible length of tendon was used for the connection; at the basic end, the hook was tied directly to the excised implantation in the cardiac wall. The lower hook was attached to a connection in the bottom of the chamber, the upper hook to a length of cold-stretched stainless steel wire (*w*) for the upper fixation. Thus, compliant connections were held at a minimum.

Initially, tension was recorded with the RCA 5734 electromechanical transducer, to which the steel wire leading into the muscle chamber was attached. For active-state duration measurements with the tension-reestablishment method of Ritchie (1954), this connecting wire passed through a hole in the core of an electromagnet relay (*r*) arranged with a stop in the relay arm which could be released at a predetermined time after the stimulus to allow a set degree of shortening before the muscle pulled on the transducer.

Subsequently, a variable capacitance transducer was used, which was designed and built by Mr. M. O. Schilling.[2] This transducer formed the bottom of the muscle chamber, and consisted of two condensor plates (*c*) and (*c'*) held taut between 12 pairs of minute coilsprings at a distance of 8 microns; the system and its connection to the chamber were filled with a high density, low viscosity silicone fluid (Dow-Corning 555). This transducer could bear up to 30 gm. of tension, corresponding to a displacement of one plate by about 1 micron. It was perfectly linear over the whole range used, and its unloaded frequency response, while not determined accurately, was far above any critical time constant encountered. The changes in capacitance were detected by the variations in the dynamic response in a tuned circuit, using the dynagage.[3] In this arrangement, the upper attachment of the muscle was free, and could be used for mechanical manipulations of muscle length such as isotonic shortening, quick stretch, or quick release, without mounting the tension transducer on a moving arm and possibly introducing vibrations and accelerometer effects. The Ritchie method for active state measurement was also carried out with this procedure, in which case the upper connection, after its release, now pulled against a fixed stop (*s*).

Recording of Shortening (Fig. 1).—A very light isotonic lever (*l*) designed according to the usual principles with miniature ballbearings (*b*) and a large lever ratio (25:1), was developed by Mr. M. O. Schilling,[2] in which the lever arm moved one plate (*p*) of a variable capacitance. The electrical variation was recorded as with the tension transducer. It displayed perfect linearity over its full range of 2 cm., and was sensitive to about 0.7 micron.

The muscle chamber and recording gages were arranged on a heavy cast iron base placed on vibration dampers. Adjustments were made with a Palmer stand rigidly mounted onto this base.

---

[3] Photocon Research Products, 421 North Altadena Drive, Pasadena. We are indebted to this company for various courtesies, including the loan of pieces of equipment during the exploratory stage of our work.

Description of Inotropic Phenomena

The Staircase Effect.—Since the major aim of this study was to elucidate the mechanisms through which inotropic changes are brought about, we have concentrated on the staircase effect as a means of securing wide variations in contractile strength with reversible physiological means. We shall first describe measurements performed on muscles operating at various frequencies of stimulation. In keeping with the classical results (*e.g.* Woodworth, 1902) we found greater force of contraction at higher frequency. In addition, however, we found that the stronger contractions are also faster, so that even the total duration of the contraction cycle becomes shorter. Variation in speed is actually an old observation (Hoffman, 1901, 1926), but its significance was not appreciated until the work of Niedergerke (1956) and the present investigation.

It is most revealing to observe this effect during the transition from one frequency of stimulation to another (Figs. 2 *a* and *b*). Upon raising the frequency it is found that the individual contractions first increase in strength without altering the duration of the twitch, until maximal strength is reached, whereupon the twitch duration decreases. During this latter phase, the twitch tension may or may not drop somewhat. In the more typical cases, the tension does not alter as the twitch duration reduces itself, but we find it instructive to point to the fewer cases in which the reduction does occur, in view of considerations regarding the duration of the active state given under the appropriate heading. Invariably the shortening of the time relations in the contraction cycle has been found in all our experiments.

All our observations on the staircase effect and other potentiation phenomena were done in the ionic medium described, in which the staircase is "normal" or "positive." The profound effects of changing the ionic composition (Niedergerke, 1956) will require separate investigation.

Post-Extrasystolic Potentiation.—Interspacing an extra systole within a regular sequence of stimuli causes the subsequent beat to be markedly strengthened (Woodworth, 1902). This strengthening (Fig. 2 *c*) always consists of an intensification of the contractile strength without marked alteration of the duration of the contraction cycle.

With or without reduction of the twitch duration, the potentiation caused by an extrasystole or an increased rhythm always results in a greater initial velocity of contraction.

The Length-Tension Diagram

Length-tension diagrams of various heart preparations have been given in the literature. Those obtained by studying whole hearts at different degrees of filling as determined by the pressure cannot be directly compared with those obtained from linear strips or other preparations of predominantly longitudinal extension (*e.g.* Lundin, 1944; Wöhlisch and Clammann, 1936). The latter diagrams

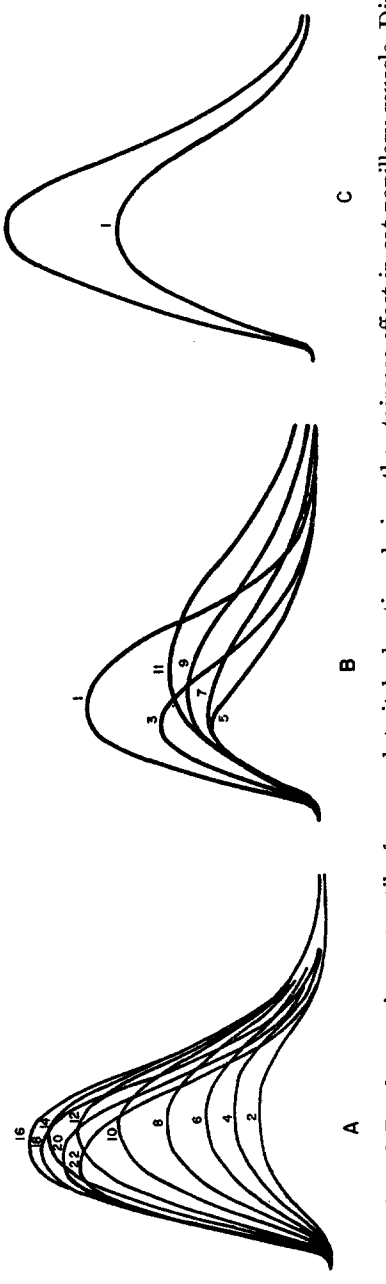

FIG. 2. A and B, changes in contractile force and twitch duration during the staircase effect in cat papillary muscle. Direct tracings of original oscilloscope records. A, after a rest of 1 hour, stimulation was started at a frequency of one per 4 seconds, and the twitches as indicated by the numbers were recorded. B, after the previous sequence, the frequency was reduced to one per 10 seconds, and the twitches were recorded during the descending staircase as indicated by the numbers. C, comparison between a normal twitch (trace 1) and one potentiated by a preceding extrasystole (trace 2). Basic rate of stimulation one per 4 seconds, at 21°C.

are comparable as such to those studied on skeletal muscle. They generally seem to differ from the typical examples of muscle in that they do not show a broad region over which the resting tension is zero or negligible, the active tension maximal and little dependent on length. On the contrary, with increasing stretch both resting and total tension continue to increase, and the active tension has a broad optimum which declines only at great extensions where the resting tensions are quite appreciable. These features, while undoubtedly of physiological significance, will complicate several aspects of the mechanical behavior, especially since no indications exist as to whether the resting tension resides in the series elastic and contractile components or in the parallel elasticity.

Our results on the papillary and trabecular muscles (Fig. 3 *a*) are in general agreement with other published data. We have, in addition, investigated the effect of stimulation frequency upon the active tension diagram, and found that, while the curves are raised when contractile strength increased they do also originate from points of decreasing length on the abscissa. Special measurements at the lowest measurable tensions were devoted to a substantiation of this latter feature (Fig. 3 *b*). The same result, less extensively investigated, also seems to apply to post-extrasystolic potentiation.

In general, we encountered contractile tensions of the order of 2 gm. per mm.^{2}, which is less than one-tenth of the figures commonly encountered among skeletal muscles. There is reason to believe that these low forces are truly representative for the muscular strengths of small hearts, in view of the mechanical advantage under which they work (Burton, 1957).

The Series Elastic Component

Our discussions on the mechanical behavior of the myocardium will be based upon the assumption that it can be represented, like skeletal muscle (Hill, 1950), as a three component system: contractile structure, series elasticity, and parallel elasticity. In regions in which the resting tension is zero or small, the parallel elastic component can certainly be ignored; we have no information as to its participation at greater extensions. The resting tension at progressively increasing stretches shows a sizable decay after establishing a new length. Such stress relaxation is not uncommon in skeletal muscles (*e.g.* Abbott and Lowy, 1957), and may indicate plasticity in the resting contractile material.

The characteristics of the series elasticity have been measured with the approach indicated by Wilkie (1956 *a*, *b*), using isotonic releases at various intervals after stimulation. Upon such a release, the undamped series elastic part shortens instantly (Fig. 4). The extent of its shortening is determined by the difference between the developed isometric tension and the isotonic load applied. Fig. 5 shows examples of tension-extension curves. Experimental variables were the strength of contraction as determined by the rhythmic frequency, the tempera-

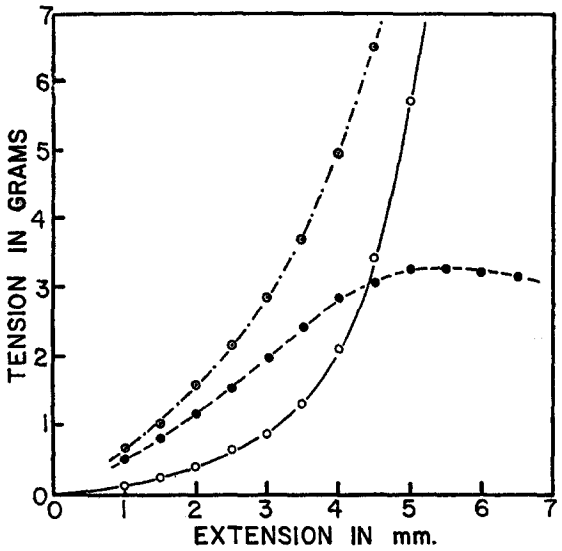

FIG. 3 A, length-tension diagrams of a trabeculae carneae preparation of the cat at 27°C. Length of the muscle 17 mm., measured at the arbitrarily accepted starting length at which the resting tension was just zero; cross-section 1.76 mm.^{2}; rate of stimulation, one per 5 seconds. ○, resting tension; ●, actively developed tension; ⊙, total action tension.

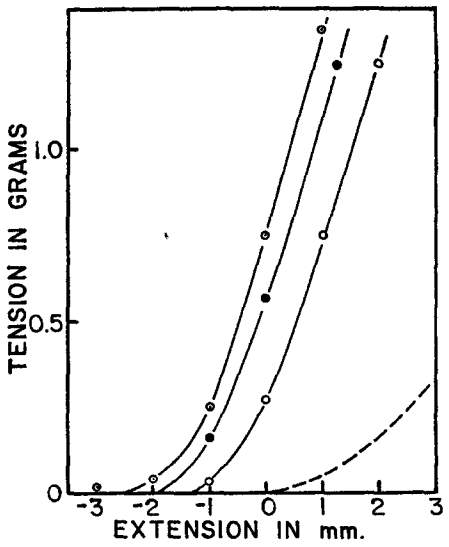

FIG. 3 B, enlarged plot of the lower region of the length-tension diagram of a trabeculae carneae preparation of the cat at 26°C. Length of the muscle 14 mm., defined as above; cross-section 2.25 mm.^{2} The broken curve gives the resting tension, as the average of several curves made in the course of the series. ○, rate of stimulation for the active curves one per 10 seconds, ●, one per 5 seconds, ⊙, one per 2 seconds.

ture, and, not illustrated, the time of release after the stimulus. These variables do not affect the results. It is true that, if the series elasticity were of thermokinetic origin, a dependence on the absolute temperature would be expected,

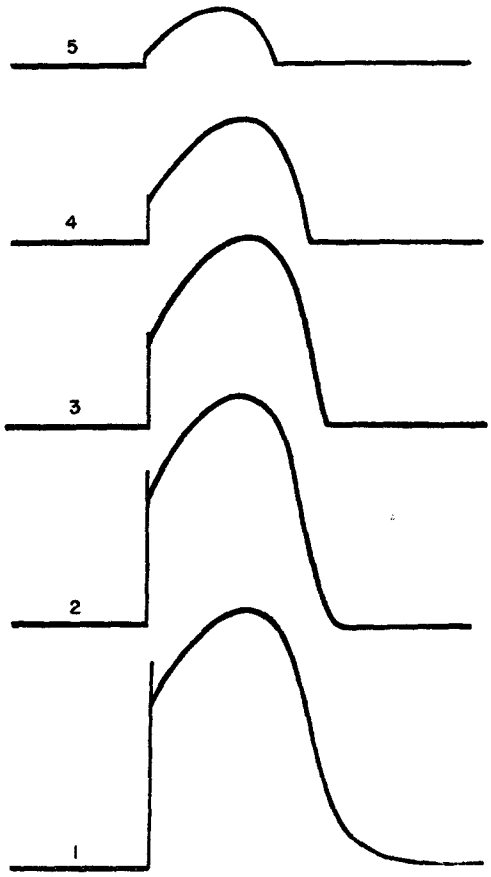

FIG. 4. Instantaneous shortening of the series elastic component upon release under varying loads. Direct tracings of original oscilloscope records, selected from a larger series on extrasystolically potentiated twitches (600 σ after preceding regular twitch), one per 2 seconds, at 28°C. Loads in the individual experiments (bottom to top) 1.54, 2.52, 4.82, 9.44, and 11.28 gm.; release 300 σ after stimulation.

but such a variation would be within the limits of detectability. The finding that the tension-stretch curves are independent of the frequency of stimulation and of extrasystolic potentiation shows that the series elastic component does not participate in the physiological variations affecting the contractile matter.

This is worth emphasizing since variations in contractile strength of the nature studied here are not easily obtained with skeletal muscle, so that this point has not, hitherto, received specific consideration.

At loads of about 2 gm. per mm.^{2}, the extension of the elastic component amounts to about 6 per cent of the muscle length. This is considerably greater

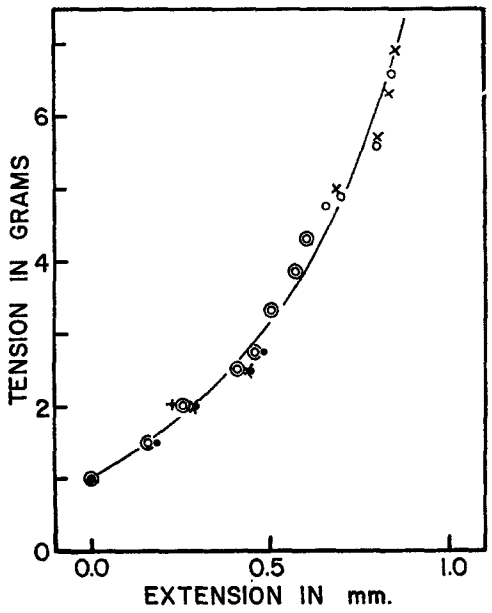

FIG. 5. Length-tension diagram of the series-elastic component of a cat papillary muscle at various temperatures and conditions of stimulation. Length 12 mm., cross-section 2.38 mm.^{2} Release 300 σ after stimulation. Meaning of symbols: ⊙, common starting point defined according to Wilkie (1956 *b*); ⊙, accumulation of points obtained with several modes of stimulation, *viz.* 28°, 1 per 2 seconds; 28°, 1 per 2 seconds, with extrasystole at 700 σ interval (○); ●, 33°, 1 per 5 seconds; ×, 33°, 1 per 5 seconds, with extrasystole at 700 σ interval, 37°, 1 per 3.2 seconds; 37°, 1 per 1.6 seconds; 19°, 1 per 5 seconds.

than the values now accepted for skeletal muscle, of the order of 2 per cent of the length as estimated from data of Wilkie (1956). It is important, therefore, to state that we have carefully evaluated the compliances of the apparatus and its connections, with the result that stretch within those parts could not have contributed measurably to the observed extensibilities.

The Duration of the Active State

A major advance in the physiology of skeletal muscle has been the development of the concept of the active state, and of methods for measuring some of

its time relations. The method of Ritchie (1954) has been employed here to follow the decay of the active state. Applied to skeletal muscle (Goffart and

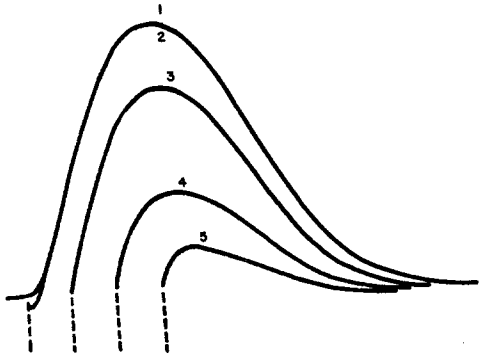

FIG. 6. Example of a normal isometric twitch and of tension redevelopment curves after releases, according to the Ritchie method (see text). Curve 1, normal twitch. Curve 2, release at the moment of stimulation. Curves 3 to 5, releases after 100, 200, and 300 σ. The muscle was stimulated once per 3 seconds at 21°C., and release experiments were done in regular sequence, interspaced by 5 normal twitches.

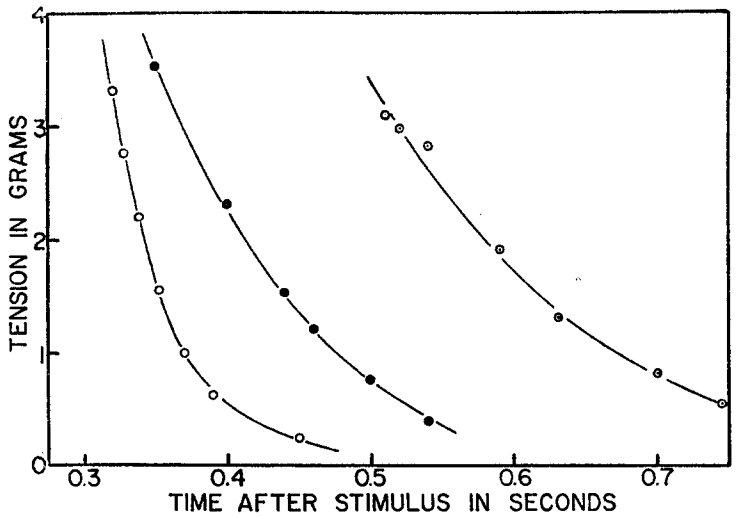

FIG. 7. Decay curves of the active state in a cat papillary muscle at 28°C.; length 12 mm., cross-section 2.38 mm.^{2} ⊙, frequency of stimulation 1 per 10 seconds; ●, 1 per 5 seconds; ○, 1 per 2 seconds.

Ritchie, 1952; Hill and Macpherson, 1954), this method has led to the result that an increased twitch tension is frequently caused by a lengthened duration of the plateau of full activity, enabling the twitch to reach a fuller extent.

Applied to the papillary muscle preparation, the method leads to curves such as those illustrated in Fig. 6, from which the decay of the active state is obtained by connecting the azimuths of the individual tension redevelopment curves. As was previously shown (Fig. 2), a higher frequency of stimulation gives stronger twitch tensions. Yet, when the decay of the active state is plotted for each of these frequencies (Fig. 7), it is found that higher twitch tensions are associated with shorter instead of longer active state durations. This statement needs some qualification. When during the development of an ascending staircase the active tension has increased, but the twitch duration had not yet shortened, the duration of the active state has not changed materially; it becomes shorter during the subsequent period in which the twitch becomes briefer. In those cases described in which the tension dropped during this interval, the lowered strength may have been a direct consequence of the shortened plateau of full activity. Those cases in which the tension remained constant may be explained by assuming that the intrinsic contractility was still growing during the abbreviation of the active state, and that the two opposing effects approximately cancelled.

In the case of extrasystolic potentiation, in which the twitch duration has not changed, the duration of the active state too is found to be unaltered. Apparently, the process of intensification is instantaneous and passes before any changes in the time of persistence of the plateau have had occasion to occur.

The Force-Velocity Relation

It is obvious from inspection of results such as those in Fig. 2, that when the contractions become stronger without lengthening their durations, the initial rate of tension rise becomes greater. This will be the case even more so when the twitch duration is shortened. If the series elastic component is not altered in the staircase phenomenon, as was previously demonstrated, this result must indicate an alteration in the shortening speed of the contractile structure.

The study of the true force-velocity relation is limited by the circumstance that in cardiac muscle the active state cannot be prolonged by tetanization, so that for afterloaded contractions with heavy weights the contractile force will have declined before the load has been lifted. Thus, the full value of the amplitude of the active state, corresponding to the tetanic tension and to P_o in Hill's terminology (*e.g.* Hill, 1950), could not be determined and no complete curve could be obtained. However, the velocities at lower loads are not influenced by this, and can be extrapolated to the maximal velocity of unloaded shortening without uncertainty.

Under afterloaded conditions, the force-velocity curve for the twitch has been determined at varying frequencies of stimulation. Results obtained with the papillary muscle at various frequencies (Fig. 8) show that as the

frequency, and hence the peak tension, increases, the initial contraction velocity increases likewise. It is concluded, therefore, that with the inotropic changes constituting the staircase phenomenon the muscle becomes inherently faster as well as stronger. For post-extrasystolic potentiation (Fig. 9),

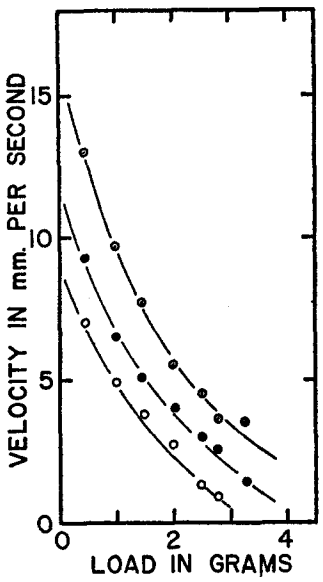

FIG. 8.

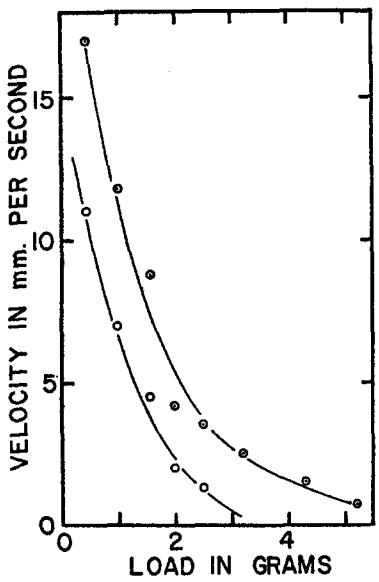

FIG. 9.

FIG. 8. Force-velocity curves, determined under afterloaded conditions. Cat trabeculae carneae preparation, 17 mm. length, 1.76 mm.^{2} cross-section, 26°C. ○, rate of stimulation 1 per 10 seconds; ●, 1 per 5 seconds; and ⊙, 1 per 2 seconds.

FIG. 9. Effect of extrasystolic potentiation upon the force-velocity relation. Experimental details as in Fig. 8. Rate of stimulation 1 per 2 seconds, with (⊙) and without (○) extrasystolic potentiation, elicited 500 σ after the preceding regular contraction.

the same result is obtained in line with the variation in the initial rate of tension development observed for this case as well (Fig. 2 *c*).

An additional difficulty in the study of afterloaded shortening originates from the special form of the length-tension diagram. In skeletal muscle, the maximum in the developed isometric force occurs at about the extension where resting tension begins to occur. By contrast, in cardiac muscle (Fig. 3) both resting and active tension increase together with stretch, and if the active force displays a clear maximum, it does so at a length where the resting tension is appreciable and may exceed the active tension considerably. The purpose of afterloading experiments is to study the relation between shortening

and load over as wide a range of loads as possible. For two reasons, this has to be done at negligible resting tension: in order to eliminate the parallel elasticity, and because the principle of afterloading implies that the load exceeds the resting tension. For heart muscle, then, this allows only a very limited range of extensions and hence of developed force. However, over the small range studied, our conclusion regarding maximal contraction velocity at zero load emerges clearly. Furthermore, the fact that diastolic pressure *in vivo* is low guarantees that our findings are not irrelevant to the physiological conditions.

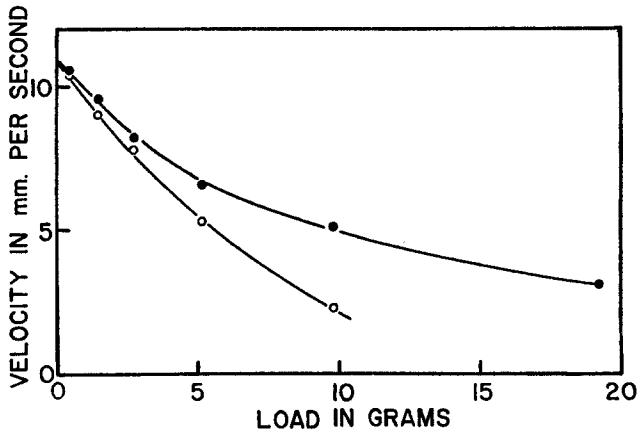

FIG. 10. Force-velocity curves under afterloaded (○) and preloaded (●) condition Rabbit papillary muscle at 27°C. Dimensions of muscle not recorded.

In order to obtain some information regarding the behavior towards heavier loads, we have also studied the force-velocity relation under preloaded conditions. This method suffers from the usual objection that both the length and the resting tension of the muscle differ for each load. Yet, this mode of experimentation is not entirely arbitrary, since, in distinction to skeletal muscle, the myocardial fibers have no defined resting or maximum length. The afterloaded curve, too, gives valid information regarding the initial shortening velocity at zero load, and should, indeed, extrapolate to the same velocity at zero force, as can be shown experimentally (Fig. 10). In addition, it provides some data on the maximal force and on those conditions of stretch that may occur in conjunction with Starling's law and in the case of ventricular dilation.

Preloaded force-velocity curves are shown in Fig. 11. Higher frequencies of stimulation give higher isometric tensions and, with afterloading, greater shortening, or lifting of heavier weights. This in itself gives no information concerning the greatest possible force of contraction, P_o (the full active state)

due to the limitations indicated above. When plotted as a force-velocity curve (Fig. 11), the preloaded shortening data give an apparent value, P_o', which might be independent of the frequency of stimulation. Whether the resting tension at such great length is borne by the parallel elasticity or by the contractile matter, the conclusion suggests itself that the variations in twitch tension are not due to variations in P_o, and hence are not caused by variations in the intensity of the active state. However, there is much uncertainty in

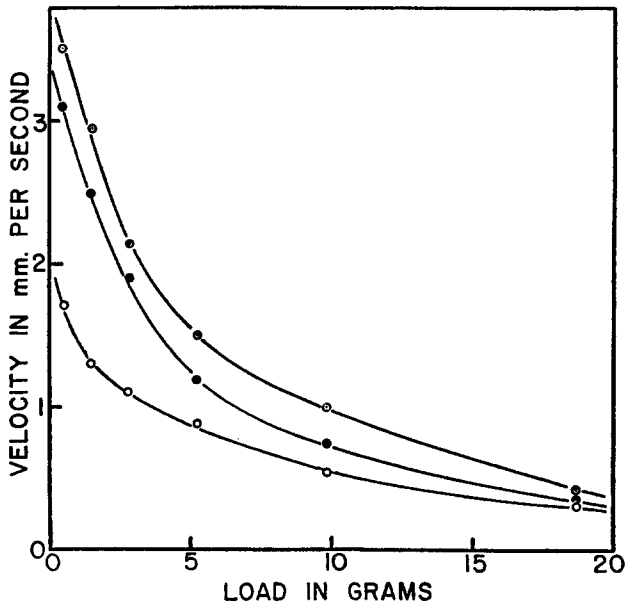

FIG. 11. Force-velocity curves under preloaded conditions. Rabbit papillary muscle at 26°C.; length 11 mm., cross-section 2.42 mm.^{2} Frequency of stimulation 1 per 10 seconds (○), 1 per 2 seconds (●), and 1 per second (⊙).

this argument, and the nature of the measurements is such that even as an experimental fact the constancy of P_o' is not established in this fashion.

The Effect of Quick Stretches

In the investigation of skeletal muscle, the amplitude of the active state has been defined as the tension the muscle develops when the active state lasts sufficiently long, that is in tetanus. The intensity of the active condition at any moment can also be defined as that tension at which the contractile component neither lengthens nor shortens. This definition is made use of in the Ritchie method for studying the decay of the active process. It has also been the basis of the original method of measuring the intensity of the active

state in skeletal muscle by the application of rapid stretches (Hill, 1953). If applied at an early moment after stimulation, before the elastic component has become appreciably stretched, this device serves, by a selection of suitable degrees of stretch, to extend the series elasticity to the point at which

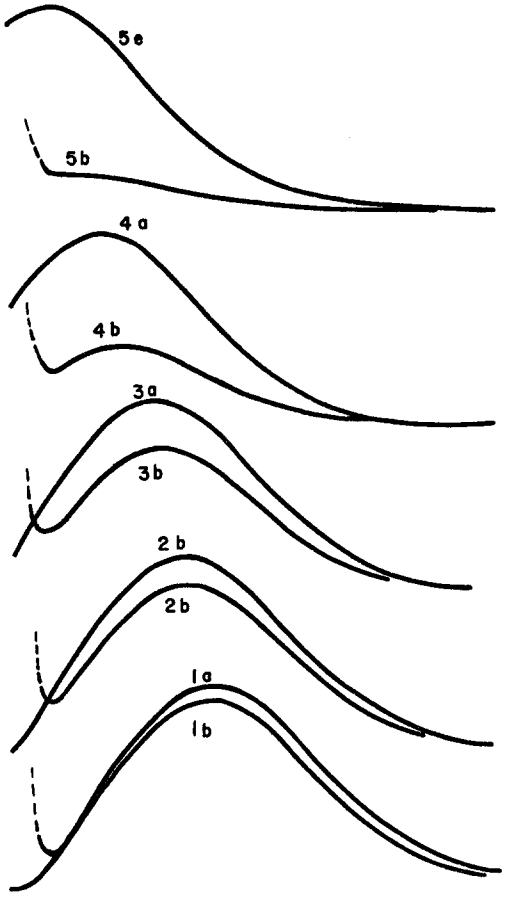

FIG. 12. Effect of quick stretches (curves *b*) upon the course of a twitch compared to a normal twitch (curves *a*). Direct tracings of original oscilloscope records. Moment of stretch (curves 1 to 5) 0, 50, 100, 200, and 300 σ after stimulation. The horizontal sweep was released at the moment of stretch, and only the descending ends of the stretch transients appear on the records. Cat trabeculae carneae, 17 mm. length, 1.76 mm.^{2} cross-section, 30°C., 1 stimulus per 3.2 seconds.

its tension just balances that of the contractile component at that time. Since in the heart tetanic contraction cannot normally be achieved, this alternative approach seemed the major remaining possibility for measuring the intensity of the active state in the present work.

In the classical experiments on frog muscle, Hill (1953) showed that stretching the sartorius during the latent period by an amount equalling the presumed internal shortening (allowing for the compliance of the connections) revealed an early attainment and subsequent maintenance of a plateau of full activity in a twitch. This was accomplished with stretches over a period of probably about 40 milliseconds, and there was no suggestion that the speed of stretch was critical as long as it was fast enough. Hence, we applied stretches of the order of a few milliseconds to papillary muscle preparations by means of a magnetically released strong spring. Such rapid stretches, if sufficiently extensive, often cause stimulation of the muscle. Muscles giving such responses at the applied degree of stretch were avoided, but in any case stretches applied after the stimulus and falling within the refractory period did not cause stimulation. In all cases (Fig. 12) it was observed that after a very early stretch the tension rises rapidly to a peak and falls quickly to almost zero. Identical transients of tension development and stress relaxation were observed with resting papillary muscles. In case of active muscles, the twitch tension redevelops after the stress relaxation process. If the stretch occurs early after stimulation, the redevelopment of tension closely follows the normal course of the twitch; with later stretches, the redevelopment stays increasingly below that during the twitch. In all cases, the immediately following regular twitch is entirely normal. It appears as if too rapid stretching temporarily destroys the active state, but interferes only passingly with the possibility of its redevelopment. Similar observations were made upon muscles potentiated by an extrasystole; these revealed the same characteristics. When attempts were made to conduct the stretches more slowly, we obtained indications that tensions greater than isometric twitches might yet be obtained in this manner, but an ergometer with controlled speeds was not available during the present work. Even in frog sartorius muscles we found that stretches faster than those employed by Hill give rise to phenomena identical with those described above. Therefore, the velocity of stretch must be selected more carefully than is generally realized. For the moment, then, this line of experimentation allows no conclusion regarding the intensity of the active state in cardiac muscle.

DISCUSSION

This investigation represents the first effort to analyze some of the fundamental mechanical characteristics of cardiac contractility, and to explain inotropic variations in terms of basic concepts such as the force-velocity relation, and the intensity and duration of the active state. Some of our conclusions were aimed at in Niedergerke's (1956) work on the staircase phenomenon in the frog heart, but were not approached experimentally.

We have clearly demonstrated that, unlike what might have been anticipated from analogies with skeletal muscle (Goffart and Ritchie, 1952; Hill

and Macpherson, 1954), a positive inotropic effect is not realized by a lengthening of the active state. On the contrary, the "plateau of full activity" is either unaltered or shortened, dependent on the circumstances.

The second positive result is that intensified contraction at a given temperature is always associated with a greater speed of tension development or a greater velocity of shortening. This leaves two possible explanations for posi-

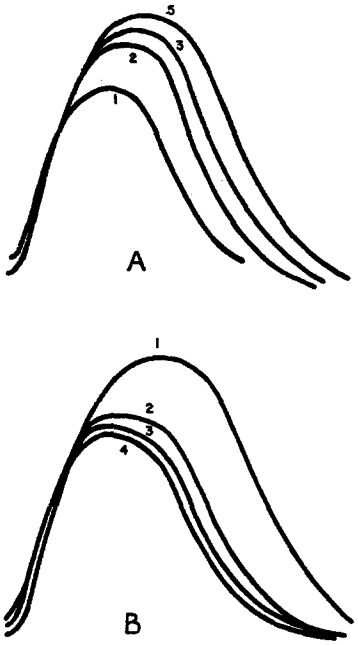

FIG. 13. Examples of the isometric responses of a cat papillary muscle showing a negative staircase phenomenon. A, sequence of transitional twitches going from 1 stimulus per 5 seconds to 1 stimulus per 2 seconds. B, opposite sequence. In this case, there appears to be no appreciable change in the initial contraction velocity, and the twitches are of longer duration when stronger, shorter when weaker. (See text.)

tive inotropy: either its mechanism consists of a fundamental alteration of the force-velocity relation, or it is caused by an intensification of the active state which automatically has an increased velocity of contraction as one of its manifestations. We wish to point out, however, that under other circumstances, such as the effect of an altered Ca concentration studied by Niedergerke (1956), these conclusions need not be valid. It appears, on the contrary, that certain other inotropic variations may indeed be caused by changes in the duration of the active state. A further illustration of this is provided by some preliminary measurements (Fig. 13) on a preparation that showed a negative staircase effect even under the conditions of our experiments. We also

believe that the problem of the relation of contractile strength to the duration of the action potential (see Cranefield and Hoffman, 1958) must be investigated with reference to the question as to which type of inotropic variation is operative.

Our observations regarding the changes in the force-velocity curve assume additional meaning in view of a problem raised by Hill (1956): is the contraction velocity for optimal efficiency constant in the heart as it is believed to be in muscle? Since the velocity-efficiency curve (Hill, 1939) can be derived from the load-efficiency and the load-velocity curves, our observations imply that at greater frequency of contraction the myocardium shifts its optimal efficiency to greater velocities of shortening. Hence, the heart adjusts its internal characteristics so that, at greater speeds of action, it is optimally efficient at greater speeds of shortening. This would constitute a basic law of cardiac dynamics, which we elaborate upon more extensively elsewhere (Mommaerts, Abbott, and Whalen, 1959).

LITERATURE CITED

Abbott, B. C. and Lowy, J., 1957, *Proc. Roy. Soc. London, Series B*, **146,** 280.

Burton, A., 1957, *Am. Heart J.*, **54,** 801.

Cattell, McK., and Gold, H., 1941, *Am. J. Physiol.*, **133,** 236.

Cranefield, P. F., and Hoffman, B. F., 1958, *Physiol. Rev.*, **38,** 41.

Feigen, G. A., Matsuoka, D. T., Thienes, C. H., Saunders, P. R., and Sutherland, C. B., 1952, *Stanford Med. Bull.*, **10,** 27.

Goffart, M., and Ritchie, J. M., 1952, *J. Physiol.*, **116,** 357.

Hill, A. V., 1939, *Proc. Roy. Soc. London, Series B*, **127,** 434.

Hill, A. V., 1950, *Proc. Roy. Soc. London, Series B*, **137,** 40.

Hill, A. V., 1953, *Proc. Roy. Soc. London, Series B*, **141,** 998.

Hill, A. V., 1956, *Brit. Med. Bull.*, **12,** 165.

Hill, A. V., and Macpherson, L., 1954, *Proc. Roy. Soc. London, Series B*, **143,** 81.

Hoffman, F. B., 1901, *Arch. ges. Physiol.*, **84,** 130.

Hoffman, F. B., 1926, *Z. ges. exp. Med.*, **50,** 130,

Lundin, G., 1944, *Acta Physiol. Scand.*, **7,** suppl. 20.

Mommaerts, W. F. H. M., Abbott, B. C., and Whalen, W. J., 1959, Selected chapters in the physiology of the heart, *in* The Structure and Functions of Muscle, (G. Bourne, editor), New York, Academic Press Inc.

Mostofsky, D., and Sandow, A., 1951, *Electronics*, **24,** 11.

Niedergerke, R., 1956, *J. Physiol.*, **134,** 569.

Ritchie, J. M., 1954, *J. Physiol.*, **126,** 155.

Rushton, W. A. H., 1930, *J. Physiol.*, **70,** 317.

Ullrich, W. C., and Whitehorn, W. V., 1956, *Circulation Research*, **4,** 499.

Wilkie, D. R., 1954, *Progr. Biophysic.*, **4,** 288.

Wilkie, D. R., 1956 *a*, *Brit. Med. Bull.*, **12,** 177.

Wilkie, D. R., 1956 *b*, *J. Physiol.*, **134,** 527.

Wöhlisch, E., and Clammann, H. G., 1936, *Arch. ges. Physiol.*, **237,** 590.

Woodworth, R. A., 1902, *Am. J. Physiol.*, **8,** 213.