Pressure-Induced Hypertrophy of Cat Right Ventricle

An Evaluation with the Force-Interval Relationship

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SUMMARY We evaluated the force-interval relationship for papillary muscle isolated from two groups of cats, one sham-operated (control group), the other having undergone pulmonary artery constriction (hypertrophy group) 18.6 ± 2.9 weeks prior to sacrifice. The right ventricular free wall muscle mass and the peak systolic right ventricular pressure were significantly greater in the hypertrophy than in the control group. The peak force and maximum rate of rise of force (F\text{max}) per cross-sectional area were not significantly different for the two groups. The qualitative features of the force-interval relationship, in particular postextrasystolic potentiation, were the same for both groups. There were quantitative differences between the groups, however. The amount of potentiation expressed, the ratio of F\text{max} of the potentiated to that of the previous regular contraction (i.e., the force-interval ratio), was significantly greater in the hypertrophied than in the control group. In both groups, the force-interval ratio was independent of muscle length, yet was altered by changing the inotropic state of the muscle (e.g., by alterations in calcium concentration). Increasing and decreasing the calcium concentration decreased and increased, respectively, the force-interval ratios in both groups. The application of these results to theories about the mechanisms underlying the alterations in mechanical performance induced by hypertrophy is discussed.

CHANGES IN THE mechanical properties of isolated cardiac muscle accompanying pressure-induced hypertrophy have been the subject of a number of investigations, but no unanimous view has yet emerged. Bassett and Gelband,1 Kaufmann et al.,2 and Cooper et al.3 reported the peak force per cross-sectional area developed by papillary muscles from hypertrophied hearts to be less than that from control hearts, whereas Pannier,4 Spann et al.,5 Grimm et al.,6 Fisher and Kavalter,7 and Bing et al.8 found no significant differences between the two groups; Kerr et al.9 found the force per muscle weight to be greater in hypertrophied hearts. Similarly, Spann et al., Bassett and Gelband, and Cooper et al. found the maximum rate of force development per cross-sectional area to be depressed in hypertrophied hearts, whereas Pannier and Fisher and Kavalter found no significant difference. Jounnott and Hatt10 and Williams and Potter11 found that, after banding, peak force and maximum rate of force development declined at first and then returned to the control values. The effect of hypertrophy on the force-velocity relationship is similarly controversial. Some investigators found the force-velocity relationship to be depressed,2,3 while others found it to be essentially the same in the two groups.5,8

We were left to wonder whether hypertrophied hearts, particularly the kind that appear normal on the basis of these traditional criteria, could be identified by any kind of mechanical measurement. One promising area in which to search for such a difference appeared to be the force-interval relationship, particularly in the transient aspects of this relationship such as postextrasystolic potentiation and negative and positive staircases. Its potential value was based in part on the significant changes in this relationship produced by a wide variety of inotropic interventions2 and the possibility that hypertrophy also would alter the force-interval relationship in a significant and distinct manner. Although the effects of hypertrophy on the steady state aspects of the force-interval relationship have been examined (Spann et al. found an effect, Pannier found none; Williams and Potter found an effect early after pulmonary artery banding, which appeared to disappear with time), no studies (other than that of Meersoon and Kapelko12) have yet explored these non-steady state aspects of the force-interval relationship.

The first objective of this study was to determine whether the development of hypertrophy is associated with significant changes in the non-steady state force-interval relationship. The second was to test whether the way the force-interval relationship of hypertrophied muscle responded to inotropic interventions, e.g., changes in calcium concentration, was the same as for normal cardiac muscle.13 Finally, we tested whether the force-interval relationship of hypertrophied cardiac muscle was independent of muscle length as has been shown for normal cardiac muscle.14
Methods

One-year-old cats (n = 30; average weight, 3.0 ± 0.1 kg) were divided into two groups. Cats the same age were used to avoid any possible effects of age on the force-interval relationship.16 Cats were anesthetized with ketamine, 20 mg/lb, intramuscularly, and the left chest opened through the fourth intercostal space. In one group a constricting band was placed around the main pulmonary artery, constricting it by 40–50% of its normal circumference. In the other group, the controls, the same surgery was performed but no band was placed around the pulmonary artery. Seven cats died in heart failure or within 15 days following surgery. Cats in the hypertrophied group (n = 6) were studied 18.6 ± 2.9 weeks and those in the control group (n = 8), 15.0 ± 2.3 weeks after surgery. All the cats were catheterized through the external jugular vein (under ketamine sedation (5 mg/lb) and local anesthesia (1% xylocaine)). A PC 350A Millar micromanometer-tipped catheter was advanced into the right heart with the aid of fluoroscopy. The right atrial and ventricular pressures were processed by a model 8805C Hewlett-Packard carrier preamplifier with the high frequency filter set at 250 Hz and recorded by a model 7700 Hewlett-Packard thermal pen writer at a paper speed of 50 mm/sec. The micromanometer was balanced and statically calibrated with a column of water at 38°C.

After catheterization, the cat recuperated for 24–48 hours before being anesthetized with pentobarbital, 25 mg/kg, intraperitoneally. The heart was removed within 30 seconds through a midline sternotomy and placed in aerated (95% O₂, 5% CO₂) Krebs-Henseleit solution16 at 38°C. A papillary muscle from the right ventricle was removed and mounted isometrically in a tissue bath pre-saturated with aerated Krebs-Henseleit solution. Papillary muscles with cross-sectional areas greater than 1.35 mm² were not used in this study. The tissue bath, the temperature control system, the force transducer, and the method of stimulation have been described previously.17 The muscles were stretched to the peak of the active tension-length relationship and allowed to equilibrate for 2 hours before the experiments were begun.

The force signal was monitored on an oscilloscope. Fused contractions were noted, to be excluded later from the data. The force signal was filtered by a Tektronix AM 402 DC differential amplifier (high frequency filter set at 300 Hz), prior to A/D conversion at a rate of 1 kHz. The data was then digitally processed with a PDP 12 computer. The digital numerical force data were smoothed (a least squares procedure, a linear fit with the fastest slope. The maximum rate of rise of force in a contraction (F_max) was determined evens every eighth contraction to ensure that the overall rate in the first and second stages of the experiment are the same. In B, we represent the second-stage experiment in which an extra contraction is introduced at a fixed extra stimulus interval (ESI) following every eighth regular contraction, and a test contraction (T) is introduced at a variable test stimulus interval (TSI) following the previous regular stimulus. The basic interval (R) was 2 seconds.

for the study. The effectiveness of the band in inducing hypertrophy was evaluated by comparing the weights of the right ventricular free wall per body weight and right ventricular free wall per left ventricular weight in the hypertrophied and control groups.

ANALYSIS OF THE F_max-INTERVAL RELATIONSHIP: EXPERIMENTAL PROCEDURE

The method used to analyze the F_max-interval relationship was similar to that designed by Johnson et al.17 to describe quantitatively the short-term or rapidly equilibrating changes in the force of contraction of rabbit papillary muscle induced by variations in the rate and pattern of stimulation. The experimental procedure was in two stages: the first determines the way F_max of a contraction depends on the interval between a contraction and the one immediately preceding it and the second determines how the interpolation of an extra contraction modifies this dependence.

The muscle was stimulated to contract at a low constant rate (20/min) and, in the first stage of the experiment, a test stimulus was interpolated regularly but infrequently between beats at the constant rate (Fig. 1A). These extra contractions were inserted infrequently enough (after every eighth contraction in the present experiment) to ensure that the timing of the test contraction relative to the preceding regular contraction had no effect on F_max of the regular contraction that immediately preceded the next test stimulus. F_max of the contraction in response to the test stimulus was plotted as a function of the time interval between the test stimulus and the preceding regular stimulus (the test stimulus interval). In the second stage of the experiment, an extra stimulus was positioned at a fixed interval from the preceding regular stimulus (the extra stimulus interval), and a test stimulus was introduced after this extra stimulus (Fig. 1B). F_max of the contraction in

\[ F_{\text{max}} \]
response to the test stimulus was plotted as a function of the interval between the test stimulus and the preceding stimulus at the regular rate. The second stage was repeated for several different (fixed) values of the extra stimulus interval. Since, in the second stage, an extra and a test stimulus must be interpolated (compared to the single stimulus in the first stage), the average rate of stimulation would vary from the first to the second stage. To eliminate this difference, in the first stage a superfused extra stimulus was interpolated between the test stimulus and the following regular stimulus (Fig. 1A).

The effects of a change of muscle length on the $F_{\text{max}}$ interval relationship was evaluated by means of an abridged version of the two-stage experiment described above. A single pair of extra stimulus and test stimulus intervals from the second stage of the above experiment was repeated throughout the abridged experiment. This allowed a reevaluation and constant updating of the same points in the $F_{\text{max}}$-interval relationship every eight beats after a change in length. Changes in the force-interval ratio (the ratio of $F_{\text{max}}$ of the test contraction to $F_{\text{max}}$ of the regular contraction that immediately preceded the extra and test stimuli) has proved to be a useful indicator of changes in the force-interval relationship. The effects on the $F_{\text{max}}$-interval relationship of a change in calcium concentration, ouabain octahydrate ($5 \times 10^{-8} \text{ m};$ Burroughs Wellcome) and norepinephrine HCl ($10^{-7} \text{ m};$ Sigma) were tested as described previously.

The results (right ventricular weights to body weight, systolic and diastolic pressures, and force-interval ratios) from the control and hypertrophy groups were compared by Student's $t$-test for unpaired groups.

**Results**

**CATHETERIZATION FINDINGS**

The mean value of the peak systolic pressures in the right ventricles of the banded group was significantly greater than that for the control group, $56 \pm 7 \text{ mm Hg}$ vs. $30 \pm 7 \text{ mm Hg}$, $P < 0.01$. In contrast, the right ventricular end-diastolic pressures for the two groups did not differ significantly, $3.8 \pm 1.5 \text{ mm Hg}$ vs. $3.0 \pm 0.9 \text{ mm Hg}$.

**NECROPSY FINDINGS**

The right ventricular free wall in the banded group was heavier (0.93 $\pm$ 0.10 g/kg body weight) than that of the control group (0.58 $\pm$ 0.04 g/kg body weight), $P < 0.03$. Expressed as a percentage of left ventricular weight, the mean right ventricular weight of the hypertrophied group was $49 \pm 4\%$ compared to $28 \pm 2\%$ for the control group, $P < 0.005$. The mean weight of the left ventricle for each of the two groups did not differ significantly ($1.9 \pm 0.15$ and $2.1 \pm 0.1 \text{ g/kg body weight}$ for the hypertrophied and control groups, respectively). Also, the mean liver weights were not significantly different for the two groups ($24.5 \pm 1.8$ and $22.8 \pm 1.3 \text{ g/kg body weight}$ for the hypertrophied and control groups, respectively). No pleural effusions nor ascites was found in any of the cats. In hearts from both groups, the smallest papillary muscle was chosen for study. The mean cross-sectional area of the papillary muscles from the hypertrophy and control groups used for the mechanical studies did not differ significantly, $0.75 \pm 0.13 \text{ mm}^2$ vs. $0.63 \pm 0.08 \text{ mm}^2$, respectively.

**MECHANICAL FINDINGS**

**The Force-Interval Relationship at a Fixed Muscle Length**

The peak tension, $F$, developed by the regular contraction in response to stimuli at the basic rate (20/min) for the hypertrophied group, was not significantly different from that for the control group ($1.0 \pm 0.2 \text{ g/mm}^2$ vs. $1.0 \pm 0.25 \text{ g/mm}^2$). Similarly, $F_{\text{max}}$ for these regular contractions at the regular rate was not significantly different for the hypertrophied than for the control group ($10.5 \pm 1.5 \text{ g/sec/mm}^2$ vs. $12.4 \pm 2.3 \text{ g/sec/mm}^2$). The time to peak tension, however, was somewhat longer for the hypertrophied than for the control groups (146 $\pm$ 7 and 132 $\pm$ 8 msec, respectively, $P < 0.005$).

Postextrasystolic potentiation (i.e., the ratio of either $F$ or $F_{\text{max}}$ for the potentiated postextrasystolic contraction to that of the regular contraction) was significantly greater for the hypertrophied than for the control group. For example, with a regular rate of 20/min and an extra stimulus interval of 275 msec, the ratio was about 30% greater for the hypertrophied group, $2.09 \pm 0.09$, than for the control group, $1.57 \pm 0.04$ ($P < 0.001$). Similarly, the ratio of $F$ of the potentiated contraction to $F$ of the regular contraction was about 30% greater for the hypertrophied group, $2.04 \pm 0.10$, than for the control group, $1.57 \pm 0.07$ ($P < 0.001$). Interestingly, this striking difference might almost have been missed if (rather than forming the above ratio) the potentiated contractions of the two groups had been compared: $F$ for the potentiated contraction was $2.0 \pm 0.04 \text{ g/mm}^2$ for the hypertrophied and $1.6 \pm 0.40 \text{ g/mm}^2$ for the control group (not significant); $F_{\text{max}}$ for the potentiated contraction was $22.05 \pm 3.80 \text{ g/sec/mm}^2$ for the hypertrophied and $19.3 \pm 4.00 \text{ g/sec/mm}^2$ for the control group (not significant).

The differences in the values of this force-interval ratio between the hypertrophied and control groups are an example of a general quantitative difference between hearts from the two groups. Typical results obtained from the two-stage experiment described in Methods are shown in Figure 2A for a papillary muscle from the control group. In the first stage, $F_{\text{max}}$ of the test contraction increased from a minimum, at the shortest test stimulus interval, to approach a maximum plateau value as the test stimulus interval was increased. This maximum value was identical to $F_{\text{max}}$ of the immediately preceding regular contraction. In the second stage, $F_{\text{max}}$ of the test contraction increased from a minimum at the shortest test stimulus interval to approach a maximum plateau value as the test stimulus interval increased. This plateau value was invariably greater than that for the first stage of the experiment, and the shorter the extra stimulus interval, the greater was the difference between the plateau values. The results obtained from muscles in the hypertrophied group (e.g., Fig. 2B), although qualitatively similar to those from the control group (in that the general shape of each curve was the same), had significant quantitative differences. In particular, the force-interval ratio was significantly higher in the hypertrophied group than in the control group. This was
The maximum rate of rise of force from the second-stage experiment in which the fixed extra stimulus interval was 275 msec, and the squares are the results from the first-stage experiment, the triangles are the results (F_max) is plotted vs. the test stimulus intervals. The circles are the results from the second-stage experiment in which the fixed extra stimulus interval was 275 msec, and the squares are the results from the second-stage experiment in which the fixed extra stimulus interval was 400 msec. Basic rate, 20/min.

true for all extra stimulus intervals tested (275, 300, 400, and 500 msec) but was most marked for the shorter extra stimulus intervals (Fig. 3; Table 1).

EFFECT OF CHANGING MUSCLE LENGTH

The F_max-interval relationship of papillary muscles from the hypertrophied group was found to be independent of muscle length in four out of four muscles. This property is demonstrated in Figure 4A in which values of F_max for the contraction at the regular rate and for the contraction potentiated by an extra systole are plotted against muscle length. In the same figure, the force-interval ratio, i.e., the ratio of these two values, is plotted against muscle length. The constancy of this ratio illustrates the general finding that the F_max-interval relationship of papillary muscles from hypertrophied hearts did not depend on muscle length.

EFFECT OF CALCIUM CONCENTRATION

An increase in calcium concentration decreased the force-interval ratio, and this modified ratio was independent of muscle length (Fig. 4B). The direction of the change (a decrease in the ratio for an increase in calcium concentration, and, conversely, an increase in the ratio for a decrease in concentration), is the same in the hypertrophied group as that exhibited by papillary muscles from the control group. Thus lowering the calcium concentration in the bathing medium for a papillary muscle from the control group mimics the effect of hypertrophy on the force-interval ratio. At each length, F_max for both contractions in the presence of 1.25 mM calcium was reduced as compared to those in 2.5 mM Ca^2+ but not by the same factor as in the 2.5 mM Ca^2+ so that the force-interval ratio was increased.

The response of hypertrophied muscle to ouabain and norepinephrine was also tested. As with normal muscle, ouabain (5 \times 10^{-8} M) potentiated all contractions of the hypertrophied muscle, but not to the same extent. For example, F_max of contractions at the regular rate was potentiated more than F_max of the plateau portion of the second stage curve (i.e., test stimulus interval, 2.5 sec), so that the force-interval ratio fell. The continued exposure to ouabain caused a progressive potentiation and drop in the ratio. The effect of norepinephrine on the force-interval relationship could not be determined since the hypertrophied muscles began to contract spontaneously even at the lowest dose tested (10^{-7} M).

Discussion

The degree of hypertrophy of hearts used in this study (as judged from the weights of the right ventricle) and the amount of arterial obstruction (as judged from the right ventricular systolic pressure) were comparable to those obtained in other studies of pressure-induced right ventricular hypertrophy. Also, F and F_max of the control muscles were comparable to those obtained in the one study (Bassett and Gelband) that used similar temperature and stimulus rate. When the papillary muscles were stimulated at a steady rate, contractions produced by the hypertrophied group could not be distinguished from those produced by the control group, either in terms of peak tension of F_max. This is in agreement with the findings of Williams and Potter (24 weeks following surgery) and of Pannier.

The disparity between the finding cited above and those of other investigators who found differences between control and hypertrophied muscle might be explained by recalling the observations of Meerson that the response to pressure loading occurs in three stages (as described by Meerson). The first stage, the "stage of damage," commences immediately after the increased load with a rapid deterioration of the "intensity of cardiac function" (e.g., F_max or F_max per muscle mass), followed by a gradual hypertrophy and concomitant restoration of the intensity of function. During the second stage, the level of hypertrophy stabilizes; the intensity of function recovers and maintains its normal level. This time course of deterioration and recovery has been beautifully demonstrated by Jouannot and Hatt and Williams and Potter. In the third stage, the stage of "gradual exhaustion," the intensity of function falls progressively, and, in spite of renewed hypertrophy, cardiac insufficiency eventually occurs.

The banded cats in this study fulfill Meerson's definition for the stable second stage (i.e., neither in the early development of hypertrophy nor in the last stage of deterioration leading to heart failure). F and F_max for the regular contraction were the same as for the control group, and, moreover, the ventricles demonstrated no apparent trend
TABLE 1  Comparative Values: Hypertrophied vs. Control Cats

<table>
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<th>S/P surgery (weeks)</th>
<th>Ratio&lt;sub&gt;75&lt;/sub&gt;</th>
<th>F (g/mm&lt;sup&gt;2&lt;/sup&gt;)</th>
<th>F&lt;sub&gt;max&lt;/sub&gt; (g/sec/mm&lt;sup&gt;2&lt;/sup&gt;)</th>
<th>Tp (msec)</th>
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<td>Hypertrophy</td>
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<td></td>
<td>Control</td>
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<tr>
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<td>Mean ± se</td>
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<td>2.09 ± 0.09</td>
<td>1.01 ± 0.20</td>
<td>10.45 ± 1.54</td>
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<tr>
<td></td>
<td>Control</td>
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<tr>
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<tr>
<td>Mean ± se</td>
<td>15.0 ± 2.3</td>
<td>1.57 ± 0.04</td>
<td>1.03 ± 0.25</td>
<td>12.38 ± 2.34</td>
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S/P surgery (weeks), the time in weeks between surgery and sacrifice; Ratio<sub>75</sub>, ratio of F<sub>max</sub> of the test contraction (test stimulus interval, 2,500 msec) to F<sub>max</sub> of the regular contraction preceding the extra contraction (extra stimulus interval, 275 msec); F, the peak tension of the regular contraction; F<sub>max</sub>, the maximum rate of rise of tension of the regular contraction; Tp, the time to peak tension of the regular contraction.

with time after banding. During this time, neither the weight nor systolic pressure measurements of the right ventricle nor the mechanical measurements, F<sub>max</sub>, time to peak tension, nor the force-interval ratio demonstrated any statistical trend with time after banding, indicating that hearts of the banded cats had also attained a stable functional state.

Cats in those studies in which hearts demonstrate progressive deterioration of F and F<sub>max</sub> were in the first or third stage of hypertrophy. These stages, characterized as they are by a deteriorated ability to develop tension, would appear to be easily detected, but what of the second pseudo-normal stage? Although subcellular changes might well be found by biochemical or histological techniques, is there any hope that this stage can be revealed by some purely mechanical measurement? The results of the present study suggest that the force-interval ratio provides such a measurement.

The possibility that the first and third stages of hypertrophy are also marked by characteristic changes in the force-interval relationship has yet to be explored. So far, only the steady state force-interval relationship<sup>4,5</sup> and the maximum potentiation produced by paired pacing<sup>6</sup> have been examined. Although this latter quantity—maximum potentiation in response to paired pacing—appears to bear a superficial resemblance to the force-interval ratio presented in this and other studies,<sup>7,11</sup> the details of the experiment are too different to permit a meaningful comparison. First, Spann et al.<sup>5</sup> measured F after prolonged paired pacing in contrast to F<sub>max</sub> of contractions following a single extra stimulus as used in this study. Second, unlike our experimental procedures for which the extra stimulus interval was standardized, they did not use the same stimulus pattern on every muscle; they maximized potentiation by using the shortest possible paired pacing interval, i.e., an interval just in excess of the effective refractory period for each muscle. Since the amount of potentiation depends strongly on the value of this interval (cf. Fig. 3), results of this kind could depend as much on the hypertrophy-induced changes in the refractory period as on the hypertrophy-induced changes in the force-interval relationship. In spite of these differences in methodology, however, their results suggest that, at least in the failing heart, the force-interval relationship might be different from that of the normal heart. They found that, in muscles from the failing heart, the ratio of F of the potentiated contractions to that of the contractions before paired pacing was induced.

FIGURE 3  Force-interval ratio obtained from both control (C) and hypertrophied (H) papillary muscles. The fixed extra stimulus intervals used to obtain these results are presented below each set of parallel bars, 275 msec, 300 msec, 400 msec, and 500 msec. The P values were significant for each set of data. The vertical bars are the standard error of the mean.
The effect of calcium concentration on the $F_{\text{max}}$-length relationship and the $F_{\text{max}}$-interval relationship for a muscle in the hypertrophied group. On the left hand ordinate of each panel is a scale for $F_{\text{max}}$, and on the right hand ordinate of each panel is the ratio of $F_{\text{max}}$ of the test contraction (closed symbols) to that of the regular contraction (open symbols) that plotted as a cross (fixed extra stimulus interval, 275 msec; test stimulus interval, 2,500 msec). The muscle length is plotted on the abscissa. In A the calcium concentration was 2.5 μM. In B the calcium concentration was 7.5 μM. The line through the crosses in each panel is the mean value. The vertical bars are the standard error of the mean.

Numerous speculations have been advanced concerning the cellular mechanisms that underlie the mechanical changes that accompany myocardial hypertrophy, although few of these speculations acknowledge the various stages of hypertrophy. Many hypotheses deal, in one way or another, with the cellular control of calcium movement, such as transmembrane calcium fluxes, the ability of the cell to pump calcium, the ability of the sarcoplasmic reticulum to bind and release calcium, or the rate of calcium pumping by the mitochondria. The present findings that the effect of hypertrophy on the force-interval ratio mimics the effects of a drop in the external calcium concentration may have some pertinence to these questions, but for the time being, speculations of this kind are too tentative. Even if the calcium concentration can be shown to be lower in the hypertrophied than in the normal heart cell, this difference might have nothing to do with the corresponding difference in the force-interval relationship. Some other changes—say, in the biochemistry of myosin or in the action potential area-frequency relationship—might be responsible. In fact, since the mechanisms underlying the force-interval relationship are themselves completely unknown, the nexus between theories about this relationship on the one hand and theories about the alteration of mechanical function induced by hypertrophy on the other hand could easily deteriorate into unbridled speculation.

Nevertheless, the results presented here have potential theoretical and applied value. For whatever metabolic, histological, and biochemical changes take place when heart muscle hypertrophies, they lead to quantitative
(rather than qualitative) changes in the force-interval relationship, at least in the key properties tested here. As with normal muscle, the force-interval relationship is independent of muscle length, and an increase or decrease in external calcium concentration causes a decrease or increase, respectively, in the force-interval ratio.

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