Cellular Versus Myocardial Basis for the Contractile Dysfunction of Hypertrophied Myocardium

Douglas L. Mann, Yoshitoshi Urabe, Robert L. Kent, Stephen Vinciguerra, and George Cooper IV

Contractile dysfunction has been demonstrated in many previous studies of experimental right ventricular pressure-overload hypertrophy; however, given the complex changes that occur both in the cardiac muscle cell and in the multiple components of the cardiac interstitium, it is not clear whether the contractile dysfunction observed is an intrinsic property of the cardiac muscle cell or whether it is the result of a mechanically normal cardiac muscle cell contracting within an abnormal interstitial environment. The purpose of the present study was to examine the contractile behavior of cardiac muscle cells, or cardiocytes, isolated from seven cat right ventricles that were pressure-overloaded by banding the pulmonary artery; right ventricular cardiocytes from seven sham-operated cats served as controls. Cardiocytes were obtained from these cats via standard cell isolation procedures; contractile function of the cardiocytes in response to graded viscous external loads was defined by laser diffraction. The cells were stimulated to contract at a frequency of 0.25 Hz, using 100-μA direct current pulses of alternating polarity. Hypertrophied right ventricular cardiocytes obtained from banded cats showed marked systolic contractile abnormalities in comparison with right ventricular cardiocytes from sham-operated cats. The peak velocity of sarcomere shortening for the control and hypertrophied cardiocytes in 1-cp superfusate was 3.6±0.2 and 2.1±0.1 μm/sec, respectively (p<0.001); the maximum extent of sarcomere shortening for the control and hypertrophied cardiocytes was 0.21±0.01 and 0.14±0.01 μm, respectively (p<0.001). Further, the time to peak shortening in the 1-cp superfusate was significantly longer for the hypertrophied cardiocytes (150.1±3.3 versus 160.4±3.7 msec; p<0.04). When the relengthening properties of the cells were examined in the 1-cp superfusate, there were significant differences between cardiocyte groups. The peak rate of sarcomere relengthening was 3.5±0.2 μm/sec in the control cardiocytes and 2.2±0.17 μm/sec in the hypertrophied cardiocytes (p<0.001). Similarly, the time to peak velocity of sarcomere relengthening (48.8±1.8 versus 57.9±2.9 msec) and the time to 50% maximal sarcomere relengthening (57.1±3.1 versus 67.1±3.1 msec) were both significantly prolonged for the hypertrophied cardiocytes (p<0.02). This study shows for the first time that the contractile defect in this model of right ventricular pressure-overload hypertrophy is intrinsic to the cardiac muscle cell itself. This finding provides a basis for further, more focused investigations designed to determine the mechanisms responsible for the contractile dysfunction observed in this form of experimental cardiac hypertrophy. (Circulation Research 1991;68:402–415)

Previous experimental studies1–8 have shown that pressure overloading of the right ventricle eventuates in a decline in contractile performance per unit mass of myocardium, even before the onset of pump failure becomes detectable for the ventricle as a whole. Despite extensive research, however, the basic mechanism or mechanisms...
responsible for the transition from initially compensatory cardiac hypertrophy into subsequent maladaptive cardiac failure remain largely unknown. One of the major problems in defining the mechanism(s) for contractile dysfunction, either in intact ventricles or in isolated myocardial segments, relates to the complexity of the myocardium, which is comprised of cardiac muscle cells, or cardiocytes, admixed with neural, vascular, and interstitial cells. Given that there are well-defined changes in the interstitium of hypertrophied myocardium that might account for abnormal cardiac contractile performance, including increases in connective tissue content, in diffusion distance from the capillary to the center of the muscle cell, and in myocardial stiffness, it becomes exceedingly difficult to attribute a change in cardiac contractile properties to a definite change in the cardiac muscle cell itself.

To provide a more focused experimental approach to the problem of defining the causes of contractile dysfunction in cardiac hypertrophy, we have begun to characterize the contractile function of isolated cardiac muscle cells, or cardiocytes, using laser diffraction methodology to measure the dynamics of sarcomere shortening in response to graded external viscous loads. The major advantage of this technique is that it permits the direct examination of the contraction of the cardiac muscle cell in the absence of any confounding cell to cell or cell to interstitium interactions. Accordingly, the purpose of the present study was to examine the contractile performance of hypertrophied cardiocytes isolated from a well-characterized feline model of right ventricular pressure-overload hypertrophy. The results of this study constitute the initial demonstration that the systolic and diastolic contractile abnormalities that are characteristic of this model are a property of the cardiocyte component of the myocardium. Thus, any accompanying interstitial changes that occur in this experimental model would be viewed as playing a contributory rather than primary role in the abnormal contractile function of the hypertrophied myocardium.

Materials and Methods

Pulmonary Artery Banding

Right ventricular hypertrophy was induced by partially occluding the pulmonary artery with a 3.5-mm i.d. band, as we have described before. Briefly, cats weighing 2.6–3.9 kg were anesthetized with ketamine hydrochloride (15 mg/kg i.m.), meperidine (2.2 mg/kg i.m.), and succinylcholine (1 mg/kg i.v.) and placed on a respirator; a left thoracotomy was performed, and a band was placed around the proximal pulmonary artery. These cats, identified as the band group, were allowed to recover for 34.7±2.5 days. A second group of cats weighing 2.5–3.9 kg was treated identically except that a suture was passed around the pulmonary artery and then removed. These cats, identified as the sham-operated group, were allowed to recover for 31.4±7.5 days.

Hemodynamic Status

At the time of study, the cats were anesthetized with ketamine hydrochloride (25 mg/kg i.m.); right heart pressures were obtained using a stiff, fluid-filled catheter attached to a strain gauge, which was inserted through the right external jugular vein and advanced into the right atrium and ventricle. Arterial pressure was monitored by a fluid-filled catheter attached to a strain gauge, which was positioned in the proximal left common carotid artery. The mid-chest position was taken as a zero reference point for pressure measurements. Arteriovenous oxygen content was used as a measure of cardiac output and was determined in duplicate by measuring simultaneous blood samples obtained from the carotid artery and the right ventricle.

Cardiocyte Isolation

The morphological, metabolic, and electrophysiological properties of the cardiocytes used in this study have been described previously. An important feature of this adult cardiocyte model that bears emphasis, particularly with regard to studies of cardiocyte mechanical function, is that feline cardiocytes remain quiescent until electrically stimulated to contract. With the exceptions noted below, the methods used to obtain reproducible yields of calcium-tolerant cardiocytes have been described previously.

After completion of the hemodynamic studies, the cats were anesthetized with acepromazine maleate (5 mg/kg i.m.) and meperidine (2.2 mg/kg i.m.), heparinized (1,000 units i.v.), paralyzed with succinylcholine chloride (2 mg/kg i.v.), intubated, and placed on a respirator. A left thoracotomy was performed, the pericardium was blunt-dissected away from the heart, and the heart was rapidly removed, placed in cold buffer solution, and weighed. The aorta was then cannulated, and the coronary arteries were perfused retrogradely for 10 minutes first with a recirculating buffer solution of the following composition (mM): NaCl 130.0, KCl 4.8, MgSO4 1.2, NaH2PO4 1.2, NaHCO3 4.0, CaCl2 0.5, HEPES 10.0, and glucose 12.5; second with a nonrecirculating buffer of the same composition but without supplemental calcium; and third with a recirculating calcium-free buffer supplemented with type II collagenase (155 units/ml) and dispase grade II (25 ng/ml). Perfusion was terminated when the heart was flaccid. The heart was removed from the cannula, the right ventricle was carefully dissected from the heart, and the right ventricle and remaining myocardium were weighed separately. The left ventricular free wall was then dissected from the heart, and the remaining myocardium was discarded. The cardiocytes from the right and left ventricular free walls were then isolated as described previously.

Evaluation of the Experimental Model

Two aspects of the right ventricular pressure-overload model used herein were unique to this study
and therefore required further evaluation. First, given that retrograde perfusion of the heart with crystalloid and collagenase solutions results in substantial edema of the heart, as demonstrated by the fact that heart weight increased approximately 1.6-fold during enzymatic perfusion, we were not able to obtain direct measurements of right ventricular weight to assess the degree of hypertrophy at the organ level. To overcome this problem, we multiplied the weight of the freshly excised cat heart by the ratio of the right ventricular weight to the total heart weight, which was obtained immediately after enzymatic digestion of the heart; this simple calculation permitted an indirect estimate of the nonedematous weight of the right ventricle. The "calculated" right ventricular weight was then used to determine the ratio of right ventricle to body weight and the ratio of right ventricular weight to tibial length. A previous study using an acute right ventricular pressure overload model has shown that beyond 3 postoperative weeks the wet to dry ratios of the hypertrophied and normal myocardium are similar.

A second consideration was whether superfusate perfusion, and hence enzymatic digestion of the right and left ventricles, would be similar in hypertrophied and nonhypertrophied tissue. We have shown previously that the quantitative capillary density, capillary surface area, intercapillary distance, and capillary diffusion distance for this model of right ventricular pressure-overload hypertrophy are not significantly different from values in sham-operated hearts without cardiac hypertrophy. Nonetheless, we considered it important to determine whether superfusate flow was similar in the hypertrophied right and nonhypertrophied left ventricles, since diminished delivery of enzymatic buffer solution to a given chamber would render the process of isolating cells from that chamber substantially more difficult. Therefore, we used \(^{141}\)Ce-labeled radioactive microspheres to measure superfusate delivery to the right and left ventricles of a nonworking Langendorff preparation. Microspheres were obtained as a stock solution suspended in a mixture of 0.01% Tween 80 and 10% dextran; 0.3 ml of the stock solution was suspended in 0.7 ml of 0.9% saline solution, such that the final volume of 1 ml contained approximately 8.1×10⁵ microspheres. The microspheres were thoroughly agitated by alternate agitation in an ultrasonic bath and vortex agitator for at least 15 minutes before injection. Control and banded hearts were excised, cannulated, and perfused in a manner identical to that described above, except that 1 minute after switching to the nonrecirculating calcium-free buffer solution, the roller pump was stopped and a 1-ml volume of suspended spheres was injected retrogradely into the perfusion apparatus at a site immediately proximal to the cannulated aorta; the roller pump was then immediately turned on, and the heart was perfused for an additional minute to ensure that all of the injected microspheres were delivered to the heart. The tissue was then fixed in 10% formalin for 3 days; after fixation, the right and left ventricular tissue was separated from the heart, and then each ventricle was divided into nine segments of approximately equal weight. The tissue samples were counted for 10 minutes in a gamma scintillation counter set at optimal window settings for the \(^{141}\)Ce emitter. Results for the left and right ventricles were determined as the average disintegrations per minute per gram total myocardium, and the final results were evaluated in terms of the ratio of right ventricular to left ventricular superfusate flow in the banded and control hearts.

**Cardiocyte Mechanics**

Laser diffraction techniques are a valid means for measuring sarcomere shortening and relengthening dynamics in isolated cardiocytes. Moreover, the basic contractile properties of cardiocytes have been shown to remain intact after the process of enzymatic digestion and cell isolation. The details of the laser diffraction technique used for measuring contractile function of isolated feline cardiocytes in our

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**FIGURE 1.** Diagram of the apparatus used for the laser diffraction method of measuring sarcomere dynamics in isolated cardiocytes. Cardiocytes were placed on a glass slide chamber on the stage of an inverted microscope. A laser light beam diffracted by a single region of the cardiocyte was projected onto two coaligned photodiode arrays situated above the cardiocyte. Each photodiode array received a first-order diffraction pattern cast by the sarcomere striations of the cardiocyte. These first-order diffraction patterns were digitally converted to obtain an electronic measurement of sarcomere length. Thus, as the cardiocyte was stimulated to contract, the velocity of sarcomere shortening could be determined as the change in sarcomere length over time.
laboratory have been described extensively; accordingly, only a brief review is provided below.

Figure 1 illustrates the laser diffraction technique used in the present study. A narrow beam of light emitted by a continuous-wave, nonpolarized helium neon laser is passed through the \( \times 10 \) objective of a modified inverted microscope and focused on a cardiac muscle cell resting on a glass slide chamber containing buffer solution. The light diffracted by the individual sarcomeres from a single cell is then projected onto two optical sensors coaligned in a detector assembly situated 2.5 cm above the cardiocyte, such that the sensors receive the first-order diffraction patterns cast by the sarcomere array. Each sensor is comprised of a linear array of 256 photodiodes, which are scanned electronically at a frequency of 1 kHz, resulting in a real-time resolution of 1 msec for the sensor array. The distance along the face of each sensor is continuously computed electronically by summing the scan time between the photodiode at the innermost edge of the array to the center of each first-order diffraction pattern cast by the cardiocyte. The center of the first-order diffraction pattern cast onto the sensors is determined electronically as the midpoint between the rising and falling edges of the first-order diffraction pattern; the edges of each diffraction pattern were set electronically by a comparator whose threshold was 10% above ambient light intensity. The distance between the first-order diffraction patterns at every millisecond was then calculated and stored in a computer. Diffraction gratings with 600, 500, and 400 lines/mm, or 1.6-, 2.0-, and 2.5-\( \mu \)m diffraction slits, were used to calibrate the distance along the optical sensors, thus permitting the conversion of the distances between the first-order diffraction patterns to be converted into sarcomere lengths in micrometers. An inverse linear relation was empirically obtained \((r=0.999)\) between diffraction slit width and diffraction distance along the optical sensors. Although diffraction gratings permit a slit resolution of 0.002 \( \mu \)m, the precision of the sarcomere length measurement cannot be better than \( \pm 0.005 \mu \)m, because fragmentation of the first-order diffraction pattern decreases its intensity.

Figure 2A shows a typical sarcomere shortening pattern from a control cardiocyte. To reduce the noise inherent in a single contraction sequence, the velocity of shortening was determined as the average of 10 successive instantaneous sarcomere lengths. As shown in panel A, sarcomere length decreased from a resting value of 1.87 \( \mu \)m to a minimum value of 1.64 \( \mu \)m; as the cell relengthened, sarcomere length progressively increased and returned to its original resting value approximately 450 msec after electrical stimulation. A second finding illustrated by panel A is that the cell remained quiescent once it returned to its original resting sarcomere length. The change in sarcomere length as a function of time was then used to derive the peak instantaneous velocity of sarcomere shortening and relengthening. Resting sarcomere length and sarcomere shortening behavior are uniform when obtained at multiple points in the cell, excluding nuclear regions. Figure 3 extends this observation to the contractile behavior of a hypertrophied right ventricular cardiocyte shortening against a viscous load, as is described below.

**Cardiocyte Loading**

We have recently developed a simple and reliable technique for defining the contractile properties of isolated cardiocytes in response to graded external loads. With this new method, cells are bathed in methyl cellulose solutions of increasing viscosity, which are considered to impose incremental external loads on the moving surface of the cell. Accordingly, viscous loading impedes cardiocyte shortening by resisting cellular shape changes during contraction. We have shown that both the rate and extent of sarcomere shortening vary inversely with increasing viscosity, while neither cell viability, resting sarcomere length, nor osmolarity is altered; also, the effects of methyl cellulose are completely reversible on restoration of normal 1-cp loading conditions. Thus, the cardiocyte viscosity–velocity relation provides a reproducible method for characterizing the contractile performance of relatively large numbers of cardiocytes isolated from a single specimen of myocardium.
The methodology and validation for the viscosity-velocity relation have been described in detail in a previous report. Briefly, 4% solutions of methyl cellulose [\( n-(\text{methoxy} \ \beta\text{-d-glucopyranosyl})\text{-d-glucose} \)] of varying polymer length were prepared by mixing granules of a given methyl cellulose polymer in deionized water at 95°C to thoroughly wet the polymer chains. To obtain a final working concentration of 2% methyl cellulose, equal volumes of 4% methyl cellulose solution and a \( \times 2 \) concentration of the Krebs solution were mixed together and then centrifuged at 1,000g to clear minute air bubbles trapped in the viscous solution. We have shown, using both a Brookfield viscometer as well as falling ball viscometry, that at 37°C a standard buffer solution has a viscosity of 1 cp and that 2% methyl cellulose solutions of increasing polymer length and average molecular weights of 17.0, 26.0, and 41.0 kDa had respective viscosities of 12, 160, and 500 cp.

Cardiocyte Evaluation

Cardiocyte viability. To be certain that the cell isolation procedure did not lead to decreased cardiocyte viability with resultant contractile dysfunction, three separate indexes of cell viability were examined for each cardiocyte isolation performed: the percentage of quiescent rod-shaped cells in 10 randomly chosen 1 mm \( \times \) 1 mm fields, the percentage of rod-shaped cells in 10 randomly chosen 1 mm \( \times \) 1 mm fields excluding 0.4% trypan blue, and the stability of the cardiocyte preparation over the course of the studies, assessed in terms of the resting diastolic sarcomere length and the extent of sarcomere shortening measured at the beginning and end of each study.

Cardiocyte morphology. Detailed morphometric analyses of the right ventricular pressure-overload model used herein have shown that a similar duration and degree of pressure overload as that used in the present study results in a 50–130% increase in cardiocyte cross-sectional area. In the present study, analysis of cell morphometrics was performed only on those cells in which contractile function was measured using the laser diffraction technique. Since these cells were chosen based on arbitrary selection criteria (see below), as opposed to being chosen at random, we recognize that these measurements should not be regarded as irrefutable evidence of cellular hypertrophy. Nonetheless, these morphometric data are critical to the comparison of contractile function studies in the hypertrophied and sham-operated cardiocytes. Photographs \((\times 400)\) were taken of quiescent cells at their resting length; cardiocyte surface area was determined by digitizing the lateral edges of the cells obtained from the resulting 35-mm negatives (final magnification, \( \times 2,800 \)). Cell length and width were determined directly from the digitized cell image by a computer program that automatically finds the maximum cell length and width.

Cardiocyte contractility. Freshly isolated cells were allowed to equilibrate for 1 hour in pH 7.4 buffer solution of the following composition (mM): NaCl 120, KCl 5.8, NaHCO\(_3\) 4.3, CaCl\(_2\) 2.5, MgSO\(_4\) 1.5, KH\(_2\)PO\(_4\) 1.4, dextrose 10.0, and HEPES 10.0; insulin (6 mg/l) was also added. After this equilibration

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

**Figure 3.** Hypertrophied right ventricular cardiocyte shortening in a 500-cp methyl cellulose solution. Panel A: Appearance of the cell when quiescent. Panel B: Appearance of the same cell at peak shortening after electrical stimulation. As shown, the extent of sarcomere shortening was uniform throughout the length of the cell; furthermore, there was no evidence of heterogeneous activation in the methyl cellulose solution, as evidenced by the lack of cardiocyte distortion during contraction.
period, an aliquot of cardiocytes was placed in a 2 cm×2 cm×1 cm plastic chamber whose sides were affixed to a glass microscope slide; the cells were then allowed to settle through the buffer solution onto the surface of the glass microscope slide that rested on the stage of an inverted microscope. The temperature of the buffer solution in the plastic chamber was monitored continuously by a microthermistor probe positioned on the bottom of the cell chamber; the thermistor was connected to a thermostated heating stage, which kept the temperature of the Krebs solution at 37.0±0.1°C. A pair of platinum wire electrodes was used to stimulate the cells using 0.25-Hz, 100-μA direct current pulses of alternating polarity with no voltage offset between pulses; the latter two stimulation conditions were used to minimize electrolysis. This stimulation frequency permitted complete relengthening of the hypertrophied and sham-operated cardiocytes between successive stimulations, as shown by the fact that resting sarcomere length remained constant throughout the stimulation protocol.

After the amount of shortening appeared stable (generally 10–15 beats), 10 contractions were sampled and averaged to yield a final profile of sarcomere length or velocity versus time during contraction. Only the following cells were analyzed: single, rod-shaped cells, unattached to either adjacent cells or debris, which contracted with each stimulus and were quiescent between stimuli. The following parameters were examined during contraction of the cell: peak velocity of sarcomere shortening (in micrometers per second), peak extent of sarcomere shortening (in micrometers), and the time to peak velocity of sarcomere shortening (in milliseconds). During relengthening of the cell the following parameters were examined: peak velocity of sarcomere relengthening (in micrometers per second), the time to peak velocity of sarcomere relengthening (in milliseconds), and the time to 50% maximal sarcomere relengthening (in milliseconds). Both the time to peak velocity of relengthening and time to 50% sarcomere relengthening were measured beginning immediately after the peak of sarcomere shortening.

After the contractile properties of the cells were examined in 1 cp buffer solution, the external load on the cell was varied by immersing the cells in Krebs–methyl cellulose solutions of differing viscosity. To avoid introducing any experimental bias, both the order in which the viscous methyl cellulose solutions were used as well as the order in which the right and left ventricular cells were studied were selected randomly on the day of the experiment. At the conclusion of the study, the contractile properties of the cells were again examined in 1 cp buffer solution and compared with the values obtained at the beginning of the study to assess the stability of the cardiocyte preparations.

Mechanisms of contractile dysfunction in hypertrophied cardiocytes. Two additional experiments were performed to define more fully the nature of the contractile defect in the hypertrophied myocardial cells. The first experiment was designed to determine whether calcium activation of the hypertrophied cells was responsible for the observed contractile defect. Accordingly, the peak velocity and extent of sarcomere shortening were examined for hypertrophied right ventricular cardiocytes and right ventricular sham-operated cardiocytes, as the calcium concentration of the superfusate was increased from 1.25 to 7.5 mM. For these studies, the cells were lightly loaded by adjusting the viscosity of the superfusate to 160 cp, since the velocity of sarcomere shortening in 1 cp buffer solution at a calcium concentration greater than 5.0 mM exceeded the limits of resolution of the laser diffraction system.

The second experiment was designed to test whether the contractile lesion in the hypertrophied cardiocytes was the result of a defect in activation of the cross-bridges; accordingly, the rate and extent of cell shortening were examined during tetanus of the cardiocyte. Cardiocyte shortening was examined under conditions that have been shown to facilitate tetanus in isolated cat papillary muscles, that is, 27°C, 10 mM caffeine, and 7.5 mM calcium. The cells were stimulated at a frequency of 10 Hz, a pulse duration of 50 msec, a stimulus strength of 40 V, and a train duration of 1,000 msec using direct current pulses of alternating polarity with no voltage offset between pulses; despite the latter two precautions, there was some evidence of electrolysis after a second stimulus train. Therefore, for the studies reported herein, a chamber of cardiocytes was stimulated one time and then discarded. A second technical difficulty pertained to using the laser optical diffraction technique to measure the very small sarcomere lengths during tetanus of the cardiocyte. Therefore, the extent of cell shortening was recorded on standard 1/2-in. videotape and stored for playback (final magnification, ×2,000); cardiocyte resting length and length at peak shortening were measured by edge detection.

Statistical Analysis

Each value is expressed as a mean±SEM. Nonpaired t tests were used to evaluate mean differences in hemodynamic parameters between banded and control cats, as well as to assess mean differences in cell morphometrics between cardiocyte groups. Two-way analysis of variance was used to evaluate differences in mean values for contractile performance between hypertrophied and control cell groups and within cell groups as a function of differing superfusate viscosities or calcium concentrations. Post-analysis of variance comparisons (Newman-Keuls test) were performed where appropriate. To adjust for any alterations in contractile performance between hypertrophied and control cardiocytes that might have arisen from inequalities in either cell morphology or initial sarcomere length alone, an analysis of covariance was performed. Before performing each analysis of covariance, a test of parallelism was performed on the two lines being compared, to guard against the possibility of incorrectly applying the covariance method. Significant differences were said to exist at p<0.05.
TABLE 1. General Hemodynamic Parameters in Banded and Sham-Operated Cats

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sham-operated (n=7)</th>
<th>Banded (n=10)</th>
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<tbody>
<tr>
<td>Recovery time (days)</td>
<td>31.4±7.5</td>
<td>34.7±2.5</td>
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<tr>
<td>Preoperative body wt (kg)</td>
<td>3.2±0.2</td>
<td>3.1±0.1</td>
</tr>
<tr>
<td>Postoperative body wt (kg)</td>
<td>3.4±0.2</td>
<td>3.3±0.1</td>
</tr>
<tr>
<td>RV systolic pressure (mm Hg)</td>
<td>25.8±2.6</td>
<td>65.7±4.7*</td>
</tr>
<tr>
<td>RV end-diastolic pressure (mm Hg)</td>
<td>2.1±0.4</td>
<td>3.4±0.3</td>
</tr>
<tr>
<td>Arteriovenous O2 difference (vol%)</td>
<td>5.1±0.5</td>
<td>4.9±0.8</td>
</tr>
<tr>
<td>Liver wt/body wt (g/kg)</td>
<td>26.0±2.2</td>
<td>26.4±1.8</td>
</tr>
<tr>
<td>Heart wt (g)</td>
<td>13.9±1.3</td>
<td>17.6±1.7</td>
</tr>
<tr>
<td>RV wt/body wt (g/kg)</td>
<td>0.58±0.1</td>
<td>1.2±0.1†</td>
</tr>
<tr>
<td>RV wt/tibial length (g/cm)</td>
<td>0.17±0.3</td>
<td>0.29±0.3†</td>
</tr>
<tr>
<td>LV wt/body wt (g/kg)</td>
<td>3.4±0.3</td>
<td>4.2±0.4</td>
</tr>
</tbody>
</table>

All data are expressed as mean±SEM. There were no significant differences in recovery time (interval between operation and death by removal of heart), preoperative or postoperative body weights, right ventricular (RV) diastolic pressure, arteriovenous oxygen differences (normal, 4.5; range, 2.1–8.3),27 liver wt/body wt ratio, total heart weights, or left ventricular (LV) wt/body wt ratio between the banded and sham-operated groups. There were, however, significant differences in the RV systolic pressure, RV wt/body wt ratio, and RV wt/tibial length ratio between the groups when mean differences were examined by a nonpaired t test.

*p<0.001 compared with sham-operated control cats.
†p<0.05 compared with sham-operated control cats.

Results

Hemodynamic Status

Three important features of the cats used in this study are summarized in Table 1. First, in the group of cats with right ventricular pressure overload, the duration and degree of the systolic pressure overload were similar to those reported in studies wherein we have shown well-defined recovery times in both cardiac mass and cardiocyte cross-sectional area,1,10,11 as well as clear-cut abnormalities of contractile function.1 There was a significant increase in right ventricular systolic pressure in the banded cats; there was no increase in the sham-operated cats. Second, the resultant pressure overload led to an increase in right ventricular mass, as evidenced by an increase in the ratio of right ventricular weight (calculated) to body weight from 0.58±0.1 to 1.2±0.1 g/kg (p<0.03) and an increase in the ratio of right ventricular weight to tibial length from 0.17±0.3 to 0.29±0.3 g/cm (p<0.04). The ratio of left ventricle to body weight and left ventricular weight to tibial length did not differ between groups, thus precluding any significant effect of postoperative changes in body weight. Third, there was no evidence for right ventricular failure, in terms of either an elevation of right ventricular end-diastolic pressure or an abnormal increase in the arteriovenous oxygen difference. Further, there was no clinical evidence for congestive heart failure, as demonstrated by the absence of pleural effusion and ascites in the pulmonary artery–banded cats.

Evaluation of the Experimental Model

The incorporation of 141Ce-labeled microspheres into the right and left ventricles of retrogradely perfused nonworking Langendorff preparations was used to evaluate the relative flow ratios in the two chambers in banded and control hearts. This study showed that the ratio of right ventricular to left ventricular perfusate flow, measured in terms of the absolute number of disintegrations per minute per gram of ventricular tissue, was at least as great as that in the left ventricle in both control and banded hearts.

Cardiocyte Evaluation

Cardiocyte viability. There was no significant difference in the percent of rod-shaped cardiocytes isolated from the two ventricles of the sham-operated cats (right ventricle, 62.2±2.5%; left ventricle, 55.4±2.6%; p=NS) or banded cats (right ventricle, 50.7±3.2%; left ventricle, 54.7±4.3%; p=NS); further, virtually all rod-shaped right and left ventricular cells excluded trypan blue, regardless of whether the cells were obtained from the right or left ventricles of sham-operated or banded cats. The stability of the cardiocyte preparations used is evident from the data presented in Table 2. As shown, the resting diastolic sarcomere lengths for all of the preparations examined were virtually indistinguishable from the beginning to the end of the study, suggesting that the integrity of the cellular membrane was maintained in the hypertrophied and control cardiocytes throughout the course of the contractile function studies (~8

TABLE 2. Stability of the Cardiocyte Preparations From Sham-Operated and Banded Cats

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sham-Operated</th>
<th>Banded</th>
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<tbody>
<tr>
<td></td>
<td>RV (n=41)</td>
<td>LV (n=41)</td>
</tr>
<tr>
<td>Sarcomere length (μm)</td>
<td>Start 1.84±0.01</td>
<td>1.84±0.01</td>
</tr>
<tr>
<td></td>
<td>Finish 1.83±0.01</td>
<td>1.83±0.01</td>
</tr>
<tr>
<td>Sarcomere shortening (μm)</td>
<td>Start 0.21±0.01</td>
<td>0.20±0.01</td>
</tr>
<tr>
<td></td>
<td>Finish 0.20±0.01</td>
<td>0.20±0.01</td>
</tr>
</tbody>
</table>

Data are mean±SEM; n=number of cells studied. For each cardiocyte group examined at the start and finish of the study, there was no significant difference in either sarcomere length or sarcomere shortening when analyzed using a nonpaired t test. Furthermore, analysis of variance indicated that there was no significant difference in the resting diastolic sarcomere lengths between cardiocyte groups at the beginning or the end of the study.
hours); further, there was no significant difference in diastolic sarcomere lengths between cardiocyte groups at the beginning or end of the study. Finally, there was no time-dependent deterioration in the contractile performance of the cells during the studies.

**Cardiocyte morphology.** Figure 4 shows the frequency distributions of cell width, length, and surface area, respectively, for both the hypertrophied (n=141) and sham-operated (n=104) cardiocytes. Each parameter was significantly larger for the hypertrophied cardiocytes (p<0.001). A second important finding shown by this figure is that despite the overall larger cell dimensions observed for the hypertrophied group, there was in fact a substantial amount of overlap in each measurement between groups. As shown, there was approximately 80% overlap in cell length and width and approximately 70% overlap in total cell surface area between the hypertrophied and sham-operated cells.

**Cardiocyte contractility.** **CARDIOCYTE SHORTENING.** Figure 2 shows the sarcomere shortening patterns for a typical sham-operated cardiocyte (panel A) and a hypertrophied cardiocyte (panel B). As shown, the extent and velocity of sarcomere shortening were both markedly less for the hypertrophied cardiocyte. Figure 5 summarizes the results for the group studies, wherein the velocity (panel A) and extent (panel B) of sarcomere shortening were examined for right ventricular cardiocytes isolated from banded (n=7) and sham-operated (n=5) cats. The major finding shown by this composite figure is that both the velocity and extent of sarcomere shortening were depressed for the hypertrophied cardiocytes; further, this finding was obtained for both unloaded (1 cp) and loaded (12–500 cp) contractions. Two-way analysis of variance showed that there were significant overall differences in the velocity and extent of sarcomere shortening between (p<0.001) hypertrophied and sham-operated cardiocytes as well as within (p<0.001) individual cardiocyte groups as a function of increasing superfusate viscosity. Further, the time to peak shortening in the 1 cp superfusate was significantly prolonged (p<0.02) for the hypertrophied cardiocytes (160.4±3.7 msec; n=57 cells) when compared with those from sham-operated controls (150.1±3.3 msec; n=41 cells).

To be certain that the isolation procedure was not responsible for the observed decrease in contractile performance of the hypertrophied cardiocytes, we compared the contractile performance of the hypertrophied right ventricular cardiocytes with that of left ventricular cells (free wall) isolated from the same heart. Although it was not the intent of this analysis to make direct comparisons between the contractile performance of cardiocytes from right and left ventricles, such an analysis serves as a useful internal control with which to assess the cell isolation procedure. That is, if the depressed contractile performance of the hypertrophied cardiocytes was a function of the handling of the myocardial preparations or of the cell isolation procedure, one would expect that the contractile performance of the right and left ventricular cardiocytes would be depressed to a similar degree, rather than being confined to the cardiocytes from the right ventricle. Table 3 shows that both the velocity and extent of sarcomere shortening of the hypertrophied right ventricular cardiocytes were significantly (p<0.001) depressed when compared with left ventricular cardiocytes isolated from the same heart.

To address the potential concern that pressure overload–induced interstitial fibrosis of the right ventricle might have rendered the process of cell isolation from that chamber relatively more difficult, such that the resulting cells from that chamber were depressed functionally, the contractile performance of right ventricular cardiocytes was examined 1 week later...
similarly, the sham-operated cardiocytes showed that there were significant differences in the velocity and extent of sarcomere shortening for the hypertrophied cardiocytes at each viscosity tested. For each viscous solution shown, from 1 to 500 cp, there were a minimum of 30 hypertrophied and 22 sham-operated cardiocytes studied. For the semilogarithmic plots given above, the relation between the velocity of sarcomere shortening and superfuse viscosity was linear for both control (r=0.98) and hypertrophied (r=0.96) cardiocytes; similarly, the relation between the extent of sarcomere shortening and the superfuse viscosity was linear for both control (r=0.99) and hypertrophied (r=0.99) cardiocytes.

After pulmonary artery banding. This particular time point was chosen based on previous data that indicated that the degree of interstitial fibrosis only becomes substantial beyond 1 week.\(^2\) Table 4 shows that the peak velocity of sarcomere shortening and the extent of sarcomere shortening were significantly \((p<0.001)\) less for cardiocytes from the heart banded for 1 week when compared with right ventricular cardiocytes from sham-operated cats. It is noteworthy, however, that the degree of depression of contractile function in the heart banded for 1 week was less than was observed in the hearts banded for 4 weeks.

**Cardiocyte Relengthening.** Figure 6 summarizes the studies wherein the peak velocity and the duration of sarcomere relengthening were compared for right ventricular cardiocytes obtained from banded \((n=7)\) and sham-operated \((n=5)\) cats. With respect to the peak velocity of relengthening, panel A shows that the peak velocity of sarcomere relengthening was substantially slower in the hypertrophied cardiocytes \((p<0.001)\). Panels B and C show, respectively, that both the time to peak velocity of sarcomere relengthening and the time to 50% maximal sarcomere relengthening were each prolonged significantly for the hypertrophied cardiocytes \((p<0.002 p<0.001\), respectively) when compared with sham-operated controls. Similar findings were obtained when the right ventricular hypertrophied cardiocytes were compared with left ventricular (free wall) cardiocytes from the same heart; that is, the peak velocity of sarcomere relengthening was 32.1±5.3% slower in the hypertrophied cardiocytes \((p<0.001)\), and the time to peak velocity of sarcomere relengthening and time to 50% maximal sarcomere relengthening were, respectively, 11.7±5.7% \((p<0.05)\) and 14.7±5.2% \((p<0.01)\) longer when compared with left ventricular control cells.

**Effect of Cell Morphology on Contractile Behavior.** Based on the large degree of overlap in cell dimensions (Figure 3), as well as the similar resting diastolic sarcomere lengths (Table 2) for the cardiocytes from the hypertrophied and sham-operated cats, we considered it unlikely that the striking differences in the shortening and relengthening properties in the hypertrophied cardiocytes were due to differences in cell morphology alone. Nonetheless, to address this potential concern, an analysis of covariance was performed to correct for any differences in contractile behavior that might have arisen because of inequalities in cell dimensions or initial diastolic sarcomere length. This analysis showed that the adjusted mean differences in the extent and velocity of sarcomere shortening, the time to peak shortening, the peak velocity of sarcomere relengthening, and time to peak velocity and 50% sarcomere relengthening for hypertrophied cardiocytes were each significantly different from sham-operated control cardiocytes, even after correcting individually for any differences in cell length, width, surface area, and initial sarcomere length. Further, identical results were obtained when an analysis of covariance was used to adjust for mean differences in the above parameters between right ventricular hypertrophied cardiocytes and left ventricular control cardiocytes obtained from the same heart.
Mechanisms of Contractile Dysfunction in Hypertrophied Cardiocytes

To determine whether the observed difference in systolic function in the hypertrophied cells was the result of a defect in calcium activation of the cell, hypertrophied right ventricular cardiocytes (n=56) and sham-operated right ventricular cardiocytes (n=56) were exposed to superfusate calcium concentrations ranging from 1.25 to 7.5 mM. Figure 7 shows that for each calcium concentration tested, both the velocity (panel A) and the extent (panel B) of sarcomere shortening were depressed for the hypertrophied cardiocytes. A further important finding shown in panel A is that the magnitude of the difference in contractile performance between the hypertrophied and control cells became even more apparent at higher calcium concentrations. Two-way analysis of variance showed that there were significant differences in both the velocity and extent of sarcomere shortening within (p<0.001) and between (p<0.001) cardiocyte groups; moreover, there was a significant interaction (p<0.02) between cardiocyte groups with respect to the peak sarcomere shortening velocity as the calcium concentration of the superfusate was increased. That is, the magnitude of the difference in the peak velocity of sarcomere shortening between hypertrophied and control cells became significantly greater at higher calcium concentrations.

To determine whether the contractile defect in the hypertrophied cardiocytes was secondary to a defect in activation of the crossbridges, we examined the rate and extent of maximal cell shortening during tetanus of hypertrophied right ventricular (n=42) and sham-operated control right ventricular (n=52) cardiocytes. This experiment showed that during a sustained, fused tetanic contraction the maximal extent of cell shortening was significantly greater (p<0.001) for control cells (24.6±0.5%) than for the hypertrophied cardiocytes (17.0±1%).

Discussion

The results of this study, in which the contractile properties of isolated hypertrophied cardiocytes were studied under simple, well-defined experimental conditions, show for the first time that the contractile abnormalities associated with experimental right ven-

Table 3. Cell Shortening in Hypertrophied Right Ventricular Cardiocytes and Control Left Ventricular Cardiocytes

<table>
<thead>
<tr>
<th>Viscous load</th>
<th>1 cp</th>
<th>12 cp</th>
<th>160 cp</th>
<th>500 cp</th>
</tr>
</thead>
<tbody>
<tr>
<td>Velocity of sarcomere shortening (% change from control)</td>
<td>-41.2±4.2</td>
<td>-35.2±3.4</td>
<td>-28.8±5.9</td>
<td>-23.5±6.8</td>
</tr>
<tr>
<td>Extent of sarcomere shortening (% change from control)</td>
<td>-19.6±3.4</td>
<td>-20.8±4.1</td>
<td>-22.6±3.9</td>
<td>-16.4±6.9</td>
</tr>
</tbody>
</table>

Data are expressed as mean±SEM of the percent change in systolic contractile performance in hypertrophied right ventricular cardiocytes compared with left ventricular cells isolated from the same feline heart. A minimum of 28 cardiocytes/group was examined for each viscous solution tested (1–500 cp). Two-way analysis variance of the raw data indicated that, for viscous loads ranging from 1 to 500 cp, there were significant differences in the peak velocity and extent of sarcomere shortening within (p<0.001) and between (p<0.001) cardiocyte groups. Further, the time to peak shortening in 1 cp buffer solution was 12.4±3.9% longer (p<0.04) for the hypertrophied right ventricular cardiocytes when compared with control left ventricular cells. In contrast to the above results, there was no significant difference in the velocity and extent of sarcomere shortening between right and left ventricular cardiocytes isolated from sham-operated hearts. Analyses of covariance confirmed that the adjusted mean differences in the velocity and extent of sarcomere shortening and contractile performance were still significantly different (p<0.001), even after correcting for differences in cell length, width, surface area, and initial sarcomere length between cardiocyte groups.

Table 4. Systolic Function in Right Ventricular Cardiocytes From Cats Banded for 1 Week and Sham-Operated Cats

<table>
<thead>
<tr>
<th>Viscous load</th>
<th>1 cp</th>
<th>12 cp</th>
<th>160 cp</th>
<th>500 cp</th>
</tr>
</thead>
<tbody>
<tr>
<td>Velocity of sarcomere shortening (µm/sec)</td>
<td>3.4±0.2</td>
<td>2.2±0.4</td>
<td>1.9±0.3</td>
<td>1.8±0.2</td>
</tr>
<tr>
<td>Banded</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sham-operated</td>
<td>3.6±0.2</td>
<td>2.7±0.1</td>
<td>2.3±0.1</td>
<td>2.0±0.1</td>
</tr>
<tr>
<td>Extent of sarcomere shortening (µm)</td>
<td>0.20±0.01</td>
<td>0.16±0.02</td>
<td>0.14±0.0</td>
<td>0.12±0.02</td>
</tr>
<tr>
<td>Banded</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sham-operated</td>
<td>0.22±0.01</td>
<td>0.18±0.03</td>
<td>0.15±0.03</td>
<td>0.13±0.03</td>
</tr>
</tbody>
</table>

Data are mean±SEM. The systolic contractile performance of cardiocytes obtained from the right ventricle of a heart banded for 1 week (n=40 cells) was compared with that of right ventricular cardiocytes obtained from sham-operated cats (data from Figure 4; n=5 hearts). As shown, the peak velocity and extent of sarcomere shortening were less for the right ventricular cardiocytes from the heart banded for 1 week when compared with right ventricular cardiocytes from sham-operated hearts. Similar differences in contractile performance were obtained when the contractile performance of the right ventricular cardiocytes from the heart banded for 1 week was compared with that of left ventricular cardiocytes from the same heart.
tricular pressure-overload hypertrophy are intrinsic to the cardiac muscle cell itself. This conclusion is supported by two major lines of evidence. First, when the peak velocity and extent of sarcomere shortening were examined for right ventricular hypertrophied and sham-operated cardiocytes, both indexes of systolic function were substantially less for the hypertrophied cardiocytes (Figure 5). Importantly, these findings were obtained regardless of whether the cells were examined in a standard buffer solution (1 cp) or loaded externally by solutions of increasing viscosity ranging from 12 to 500 cp. In addition, the time to peak shortening was significantly prolonged for the hypertrophied cardiocytes. Second, when cardiocyte relengthening properties were examined, the data showed that, in comparison with cells from sham-operated control cats, the peak velocity of sarcomere relengthening was significantly slower and the time to peak velocity and 50% maximal sarcomere relengthening were each significantly prolonged for the hypertrophied cardiocytes (Figure 6). It should also be recognized that the above differences in cardiocyte shortening and relengthening did not appear to be due to obvious differences between groups in terms of cell viability or stability (Table 2), the isolation procedure itself (Table 3), or differences in cell dimensions between hypertrophied and sham-operated cardiocyte groups.

Taken as a whole, the above results show that the contractile abnormalities of hypertrophied myocardium are intrinsic to the cardiac muscle cell itself and are not a property of a mechanically normal cardiac muscle cell contracting within an abnormal interstitial environment. Indeed, we observed contractile dysfunction in our right ventricular hypertrophied cardiocyte model as early as 1 week after pulmonary banding (Table 4), at a time when abnormalities of the myocardial interstitium have been reported to be minimal.28

**Contractile Dysfunction in Experimental Right Ventricular Hypertrophy**

For the right ventricles of small mammals exposed to an acute pressure overload, the preponderance of data1–8,29,30 indicates that the contractile performance per unit mass of hypertrophied myocardium eventually becomes compromised. Earlier studies where these results were not obtained involved only modest degrees of hypertrophy.31 One study,32 although flawed by the use of experimental animals with quite variable degrees of cardiac hypertrophy and by the use of large superfused papillary muscle preparations in which metabolic support by diffusion was questionable, suggested that the contractile defect might be the result of a transient acute injury produced by the abrupt fixed-pressure overload and that the hypertrophied right ventricular myocardium contracts normally after recovery from this phase. A possible morphological basis for this injury phase was suggested by a study in which histological examination of severely overloaded myocardium revealed multifocal areas of degeneration and necrosis.33 However, some recent studies using chronic, progressive pressure overloading, in which there was no evidence of histological injury, found a progressive decrement in contractile performance per unit mass of isolated feline cardiac muscle,34 although this may not be the case for the rodent.35 Thus, it would appear that contractile dysfunction is an intrinsic property of substantial feline right ventricular pressure-overload hypertrophy. However, the important mechanistic question of the specific nature of the contractile defect in experimental right ventricular pressure overload has not been resolved by existing studies.

Important to the above discussion, therefore, is the observation that experimental volume overloads do
not lead to the onset of contractile dysfunction in the cat right ventricle, despite a duration and degree of hypertrophy comparable to that used in parallel studies of pressure-overload hypertrophy in the cat right ventricle, wherein such dysfunction does occur. This dichotomy in contractile behavior in response to differing hemodynamic overloads suggests that the development of contractile dysfunction is not an intrinsic property of hypertrophied myocardium per se, but rather the result of a particular interaction between a given type of hemodynamic overload with a given ventricular chamber. Inasmuch as there are marked quantitative and qualitative differences in the composition of the interstitium in pressure- and volume-overloaded myocardium, the question then arises as to whether the contractile dysfunction that occurs during some forms of hypertrophy is intrinsic to the cardiac muscle cell itself or whether it is a property of cardiac tissue.

Although the potential contributory role of the myocardial interstitium in modulating the mechanical performance of the heart has long been recognized, several recent studies have refocused investigative interest on the importance of the interstitium with respect to its influence on the mechanical characteristics of hypertrophied myocardium. germane to this discussion is the fact that specific changes have been identified in several major interstitial components of hypertrophied myocardium, including quantitatively and qualitatively important changes in the volume composition of type I and type III collagen as well as decreased capillary density and increased capillary diffusion distance. Thus, it is likely that one or more defects in cardiac tissue components or accumulation of ions in the extracellular spaces may contribute to the genesis and maintenance of contractile dysfunction in experimental cardiac hypertrophy. Notwithstanding these potentially important contributions of the interstitium, the results of this study show clearly that the characteristic abnormalities of systolic function in right ventricular pressure-overload hypertrophy are an intrinsic property of the cardiac muscle cell itself and are not dependent on interstitial abnormalities. Indeed, using a model identical to that used in the present study, we have shown in a previous study that for isolated papillary muscles there was a decrease of approximately 50% in the peak velocity of unloaded shortening and a decrease of approximately 30% in the peak extent of unloaded shortening (Figure 1), whereas in the present study of isolated cardiocytes there was a decrease of approximately 42% in the peak velocity of unloaded shortening and a decrease of approximately 30% in the peak extent of unloaded shortening. Thus, this study has identified a well-defined contractile defect for hypertrophied cardiocytes that appears both qualitatively and quantitatively similar to that found in papillary muscles from the same model.

Mechanisms of Contractile Dysfunction in Right Ventricular Hypertrophy

While it was not the primary intent of this paper to define fully the nature of the contractile defect in our hypertrophied right ventricular cardiocyte model, two separate experiments were conducted to explore a potential contributory role for abnormal calcium metabolism.

The first experiment, wherein the extent and velocity of sarcomere shortening were examined as a
function of increasing superfusate calcium concentrations, that for each calcium concentration tested, both the velocity and extent of sarcomere shortening were depressed for the hypertrophied cardiocytes (Figure 7). More revealing was the finding that the magnitude of the difference in peak shortening velocity between hypertrophied and control cells became significantly greater at higher calcium concentrations. If the defect in the hypertrophied cardiocytes were solely a function of defective calcium activation of the cell, we would have predicted that the contractile performance of the hypertrophied and control groups would have become less apparent at higher calcium concentrations. These latter findings are in agreement with those reported by Gwathmey and Morgan,4 who examined peak isometric tension in ferret right ventricular papillary muscles from control and pressure-overloaded hearts as a function of increasing superfusate calcium concentrations. These investigators showed that as the superfusate calcium concentration was increased, the magnitude of the difference in peak isometric tension between control and hypertrophied muscle became even more apparent. Gwathmey and Morgan4 showed further that the acqurin “fractional luminescence” signal was not significantly different in the hypertrophied and control groups, suggesting that the availability of intracellular calcium for activation was not different between hypertrophied and control groups.

In the second experiment, we examined the rate and extent of maximal cell shortening of hypertrophied and control cardiocytes under experimental conditions that produce tetanus in the papillary muscle preparation.25 This study showed that during constant activation of the crossbridges, the extent of cell shortening was depressed significantly for hypertrophied cardiocytes. Thus, although the above two experiments were not intended to be exhaustive, they do permit future studies to be directed toward the primary mechanism(s) for the contractile defect in this model. That is, the decreased contractile performance for the hypertrophied cardiocytes in right ventricular pressure overload is unlikely to be due entirely to decreased sensitivity of the myofilaments to calcium or decreased availability of intracellular calcium for activation of the myofilaments.4 Instead, it would appear that the defect resides in an inability to form crossbridges or in the inability of the activated crossbridges to produce a normal mechanical result.

Summary

Previous experimental studies1–8,29,30 have shown that pressure overloading of the right ventricle leads to contractile dysfunction that is evident both at the level of the intact ventricle and at the level of the isolated papillary muscle. This study shows for the first time that the well-defined contractile dysfunction observed for this model of experimental pressure-overload hypertrophy is an intrinsic property of the cardiac muscle cell itself. Although this study does not obviate any potentially important contributory role for the myocardial interstitium in terms of either the genesis or maintenance of contractile dysfunction in cardiac hypertrophy, it does suggest that it is not necessary to implicate abnormalities of the myocardial interstitium to explain the characteristic abnormalities of shortening and relengthening observed for experimental cardiac hypertrophy. Accordingly, the results of this study should provide a basis for further more focused and mechanistic studies designed to elucidate the basic cellular and molecular changes responsible for contractile dysfunction in experimental cardiac hypertrophy.

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