Reversible Alterations in Excitation-Contraction Coupling during Myocardial Hypertrophy in Rat Papillary Muscle

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SUMMARY. To investigate the possible role of an alteration in excitation-contraction coupling in cardiac hypertrophy, we compared simultaneously recorded action potentials along with isometric or isotonic contractions of normal and hypertrophied papillary muscles. Hypertrophy was produced by renal hypertension in rats. Hypertrophied papillary muscles were taken from rats that had been hypertensive for 10 [HBP (10)] or 20 [HBP (20)] weeks. Regression of changes induced by hypertrophy was studied in rats that had been hypertensive for 10 weeks and then made normotensive for 10 weeks by removal of the ischemic kidney. Papillary muscles from age-matched, sham-operated rats [SHAM (10), SHAM (20)] were used as controls. We found that HBP (10) rats had significantly longer action potentials than SHAM (10) rats and that difference in the action potential duration recorded during isotonic and isometric contractions was significantly different for SHAM (10) and HBP (10) rats. Peak developed tension was the same in HBP (10) and SHAM (10) muscles, but the duration of isometric contraction and time-to-peak shortening were longer in HBP (10) muscles. Similarly, whereas the peak tension was the same in HBP (20) and SHAM (20) muscles, the duration of the action potential and isometric contraction, as well as the time-to-peak tension, was longer in HBP (20) muscles. The longer values for action potential duration, isometric contraction, and time-to-peak tension in HBP (20) muscles returned to SHAM values in HBP (R) muscles. The longer action potential duration, isometric contraction, and time-to-peak tension in HBP (20) muscles did not correlate significantly with any of the contractile parameters in HBP (20) muscles. Remarkably, in HBP (R) preparations a significant correlation was restored between action potential duration and three of the four contractile parameters. The results of this study suggest that reversible cardiac hypertrophy is associated with reversible alterations in excitation-contraction coupling. The reversibility of the mechanical and electrical alterations that accompany hypertrophy suggests, in turn, that cardiac hypertrophy is an adaptive process. (Circ Res 51: 189-195, 1982)

PREVIOUS studies have reported that cardiac hypertrophy induced by pressure overload is associated with alterations in mechanical and electrical properties. The results of these studies have varied according to the model used to induce hypertrophy and the species studied (see Discussion for references). Only five of these studies involved measurement of mechanical and electrical properties in the same model and species, and in two of those studies only one parameter of mechanical performance was reported. Nevertheless, the results of some of these studies were interpreted as suggesting that excitation-contraction coupling could be altered in cardiac hypertrophy.

To investigate further the possible role of an alteration in excitation-contraction coupling in cardiac hypertrophy, we compared simultaneously recorded mechanical and electrical activity of normal and hypertrophied papillary muscles. The results reported in this paper are in accord with the view that excitation-contraction coupling is reversibly altered in cardiac hypertrophy induced by renal hypertension in the rat.

Methods

Male Wistar rats (Charles River) weighing 175-200 g were made hypertensive by placing a sliver clip with a 0.25-mm aperture around the left renal artery. The contralateral kidney was left untouched. Systolic blood pressure was measured with a tail cuff sphygmomanometer under light ether anesthesia before clipping, and weekly thereafter (Maitresello and Matscher, 1969). Rats were considered hypertensive when systolic blood pressure ≥150 mm Hg. This occurred within 3-4 weeks after clipping, and elevated blood pressure persisted until the time of the study.

Animals were anesthetized with ether. The hearts were rapidly excised and placed in oxygenated Tyrode's solution.
Left ventricular papillary muscles were removed and suspended horizontally in a myograph. We used only muscles with cylindrical uniformity and with a cross-sectional area ≤1.2 mm² to ensure adequate oxygenation of central fibers (Pool et al., 1968; Whalen et al., 1967). The muscles were superfused continuously with Tyrode's solution of the following composition in mm/liter: Na⁺, 151.3; Ca²⁺, 2.4; K⁺, 4.0; Mg²⁺, 0.5; Cl⁻, 147.3; H₂PO₄⁻, 1.8; HCO₃⁻, 12.0; dextrose, 5.5. This solution was maintained at 30°C and gassed with 95% O₂-5% CO₂. Muscles were field stimulated with bipolar electrodes at a frequency of 0.1 Hz and the stimuli were isolated from ground. The stimulating electrodes were made by removing 1 cm of the Teflon coating on each wire from their ends. The stripped ends were placed parallel to the long axis of the muscle.

The non-tendinous end of the papillary muscle was inserted into a spring-loaded stainless steel clip which was mounted at the end of a micrometer assembly that permitted adjustment of external muscle length. The tendinous end was tied to a light steel wire with a short length of silk. This wire was attached by a hook to the lever of a servo-controlled galvanometer (Cambridge Technology). Control circuitry permitted operation in either afterloaded isotonic or isometric modes. The position of the lever was measured by a variable capacitor at the rear of the galvanometer's moving iron core. Force at the tip of the lever was determined by scaling and amplifying the error signal produced in the position-servo section of the control circuitry during the contraction. The force signal was compared with the simultaneously derived force signal from a force transducer (Kistler-Morse, DSC-3) connected to the non-tendinous end of the papillary muscle. There was no phase lag or difference in time characteristics between these two signals. Therefore, during equilibration, the muscle contracted isometrically at a resting tension of 1 g. The length-tension curve was determined from an initial length of Lmax according to the manufacturer's specifications. The relationship between force (load) and maximum length of each muscle.

Active and passive length-tension curves were obtained after at least 90 minutes of equilibration in the tissue bath. During equilibration, the muscle contracted isometrically at a resting tension of 1 g. The length-tension curve was obtained by reducing muscle length (7.0 ± 0.38 mm, mean ± s) in 0.1-mm steps from the length associated with maximum developed force (Lmax) to approximately 88% of Lmax. The relationship between force (load) and maximum velocity of shortening for a series of afterloaded contractions was established from an initial length of Lmax. Total fractional torque of the servo-controlled lever is less than 5 mg-cm according to the manufacturer's specifications.

Electrical recordings were obtained with microelectrodes filled with 3% KCl. Transmembrane potential was measured as the voltage difference between the intracellular electrode and a sintered Ag/AgCl ground electrode immersed in the fluid perfusing the tissue. At the completion of each experiment, the muscle length at Lmax was measured and the muscle was blotted dry and weighed. The cross-sectional area of the muscle was calculated by assuming it was a cylinder with a specific gravity of 1.0.

Study Design

Five-week-old male Wistar rats were obtained from Charles River Farms. At 6 weeks of age, 70 rats underwent clipping of the left renal artery. Hypertension was produced in about 75% of all clipped animals within 3–4 weeks after renal artery constriction. At 10 weeks after the onset of hypertension, hypertensive animals (HBP (10)) were removed for mechanical and electrical study. Age-matched, sham-operated rats (SHAM (10)) from the same initial groups were used as controls. In Sham-operated animals, the left kidney was isolated but a clip was not placed on the left renal artery.

In addition, the mechanical and electrical effects of a reduction in systolic blood pressure were studied in previously hypertensive rats. At 10 weeks after the onset of hypertension, the left kidney of a group of rats was surgically removed (Thurston et al., 1980). Blood pressure was monitored weekly for 10 weeks after surgery. After 10 weeks of normotension (systolic blood pressure ≤150 mm Hg), the mechanical and electrical behavior of left ventricular papillary muscles from these rats (HBP (R)) was compared to that of rats 20 weeks post-sham operation (SHAM (20)) and rats that had hypertension for 20 weeks (HBP (20)).

Data Analysis

The following mechanical parameters were measured: peak isometric developed tension, resting tension, time-to-peak isometric tension, time-to-1/2 isometric relaxation, peak shortening, and time-to-peak shortening. The following action potential parameters were measured: total amplitude, resting membrane potential, and duration to 50% (APD₅₀) and 75% (APD₇₅) of complete repolarization. The result reported for each action potential parameter is the mean value from three separate impalpations along the length of each muscle.

Measured data were analyzed by one-way analysis of variance and the Scheffé multiple comparison test (Snedecor and Cochran, 1980) or by two-way analysis of variance. Correlation coefficients were determined by linear regression. A P value of <0.05 was considered statistically significant.

Results

Table 1 summarizes the characteristics of the experimental animal groups. The mean systolic blood pressure of HBP (10) and HBP (20) rats was significantly higher than that of SHAM (10) and SHAM (20) rats, respectively. The systolic blood pressure of HBP (R) rats returned to a value similar to that of SHAM (20) rats and significantly lower than that of HBP (20) rats. The elevated level of systolic blood pressure was accompanied by a significant increase in the mean

<table>
<thead>
<tr>
<th>Characteristics of Groups of Experimental Animals</th>
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<tbody>
<tr>
<td>Body wt</td>
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<tr>
<td>(g)</td>
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<tr>
<td>---------</td>
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<tr>
<td>SHAM (10)</td>
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<td>HBP (10)</td>
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<tr>
<td>SHAM (20)</td>
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<td>HBP (20)</td>
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<tr>
<td>HBP (R)</td>
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</table>

Data are given as mean ± s; n = 8 for each group. For body weight, P < 0.01 for HBP (10) vs. SHAM (10); for heart weight and systolic blood pressure, P < 0.01 for HBP (10) vs. SHAM (10), HBP (20) vs. SHAM (20), and HBP (20) vs. HBP (R).
heart weight of HBP (10) and HBP (20) rats as compared to that of SHAM (10) and SHAM (20) rats. The mean heart weight of HBP (R) rats was significantly higher than that of SHAM (20) rats. The mean body weight of HBP (10) rats was significantly different from SHAM (10) rats, and the mean body weight of HBP (20) rats was not significantly different than that of SHAM (10) and SHAM (20) rats. The body weight of HBP (R) rats was similar to that of SHAM (20) rats.

Figure 1 shows typical tracings of isometric tension and simultaneously recorded action potentials from SHAM (20), HBP (20), and HBP (R) muscles. The action potential recorded from the HBP (20) preparation is substantially longer than that recorded from the SHAM (20) muscle. The prolonged action potential of the HBP (20) muscle is accompanied by an isometric contraction which is similar in peak magnitude to that of the SHAM (20) muscle. However, a longer time is required to reach this level of peak tension. In contrast, the action potential and isometric contraction recorded from the HBP (R) muscle are very similar to control traces.

The results of a series of experiments of the kind seen in Figure 1 are summarized in Tables 2 and 3. Table 2 shows that HBP (10) rats have significantly longer action potentials than SHAM (10) rats and that the action potentials recorded during isotonic contractions are significantly shorter than those observed during isometric contraction. The fact that a significant interaction is present between groups and type of contraction indicates that the significant difference is probably between isometric and isotonic contractions of HBP muscles. There was no significant difference in the values for resting membrane potential [SHAM (10) = 83 ± 3 mV; HBP (10) = 83 ± 3 mV] or amplitude [SHAM (10) = 110 ± 4 mV; HBP (10) = 115 ± 5 mV]. Table 3 shows that developed tension was virtually the same in HBP (10) and SHAM (10) muscles but that all the timing parameters of tension development, relaxation, and shortening were prolonged in HBP (10) muscles. Resting tension was not significantly different in HBP (10) and SHAM (10) muscles.

Table 2 also shows that the action potential prolongation observed in hypertrophied fibers reverses after regression of hypertrophy. Thus, action potentials of

**TABLE 2**

<table>
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<tr>
<th></th>
<th>APD&lt;sub&gt;30&lt;/sub&gt; (msec)</th>
<th>APD&lt;sub&gt;70&lt;/sub&gt; (msec)</th>
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<tbody>
<tr>
<td></td>
<td>Isometric</td>
<td>Isotonic</td>
</tr>
<tr>
<td>SHAM (10)*</td>
<td>23.8 ± 4.4</td>
<td>21.0 ± 3.8</td>
</tr>
<tr>
<td>HBP (10)*</td>
<td>61.6 ± 6.6</td>
<td>52.9 ± 6.5</td>
</tr>
<tr>
<td>SHAM (20)f</td>
<td>26.9 ± 4.0</td>
<td>22.9 ± 3.6</td>
</tr>
<tr>
<td>HBP (20)f</td>
<td>70.0 ± 6.1</td>
<td>60.3 ± 6.7</td>
</tr>
<tr>
<td>HBP (R)f</td>
<td>27.5 ± 5.1</td>
<td>24.4 ± 4.7</td>
</tr>
<tr>
<td>F value</td>
<td>185.01</td>
<td>135.70</td>
</tr>
<tr>
<td>F probability</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
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</table>

* Data are given as mean ± se; n = 8 for each group. Degrees of freedom = 1,14. Two-way analysis of variance gave F values of <0.0001 for isometric vs. isotonic contractions, for SHAM (10) vs. HBP (10), and for interaction between group and type of contraction.

f Data are given as mean ± se; n = 8 for each group. Degrees of freedom = 2,21. Scheffe multiple comparison test gave P values of <0.0001 for HBP (20) vs. SHAM (20) and HBP (R) and P values of 0.8450 to 0.9961 for SHAM (20) vs. HBP (R) for each parameter.
HBP (20) muscles are significantly longer than those of both SHAM (20) and HBP (R) muscles during both isometric and isotonic contractions. In contrast, the duration of action potentials of HBP (R) and SHAM (20) muscles is almost the same during both isometric and isotonic contractions. There was no significant difference in the values for resting membrane potential [SHAM (20) = 84 ± 4 mV; HBP (20) = 82 ± 3 mV; HBP (R) = 79 ± 3 mV] and amplitude [SHAM (20) = 110 ± 5 mV; HBP (20) = 113 ± 4 mV; HBP (R) = 109 ± 4 mV]. Table 3 shows that the contractile alterations observed in hypertrophied muscles also reverse when hypertrophy regresses and that even after 20 weeks of hypertension developed tension does not change. Thus, the prolonged course of tension development, relaxation, and shortening seen in HBP (20) muscles reverses in HBP (R) muscles which have timing parameters similar to SHAM (20) muscles. No significant difference was observed in resting tension between the three groups of experimental rats.

Previous work (see Discussion for references) indicates that the time course of membrane depolarization can influence the characteristics of the contractile response. Therefore, we reasoned that a rough way to test for a possible physiological relationship between the time course of membrane potential and the nature of the contractile response was to establish whether or not there was a correlation between the time course of the action potential and the parameters that characterize contraction. To accomplish this test with our data, we plotted APD50 and APD75 against four parameters of contraction: peak developed tension (Fig. 2), time-to-peak tension (Fig. 3), time to half relaxation (Fig. 4), and time to peak shortening (Fig. 5). Statistical analysis of these data for SHAM (10) and SHAM (20) muscles showed a significant correlation between all four parameters of contraction and action potential duration. In contrast, HBP (10) muscles showed a significant correlation between only two contractile parameters and action potential duration. Even more striking was the lack of a significant correlation between action potential duration and any

**TABLE 3**

Mechanical Parameters of Animal Groups

<table>
<thead>
<tr>
<th></th>
<th>TTP (msec)</th>
<th>T1/2R (msec)</th>
<th>RT (g/mm²)</th>
<th>DT (g/mm²)</th>
<th>TPS (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SHAM (10)*</td>
<td>129 ± 9.0</td>
<td>162 ± 10.1</td>
<td>1.94 ± 0.3</td>
<td>7.2 ± 0.7</td>
<td>133 ± 6.1</td>
</tr>
<tr>
<td>HBP (10)*</td>
<td>165 ± 14.5</td>
<td>180 ± 18.1</td>
<td>2.01 ± 0.4</td>
<td>7.0 ± 0.4</td>
<td>174 ± 9.6</td>
</tr>
<tr>
<td>SHAM (20)f</td>
<td>134 ± 9.2</td>
<td>166 ± 9.9</td>
<td>1.97 ± 0.3</td>
<td>7.4 ± 0.5</td>
<td>138 ± 6.3</td>
</tr>
<tr>
<td>HBP (20)f</td>
<td>174 ± 16.6</td>
<td>190 ± 18.9</td>
<td>2.05 ± 0.3</td>
<td>7.3 ± 0.8</td>
<td>185 ± 7.6</td>
</tr>
<tr>
<td>HBP (R)t</td>
<td>134 ± 10.0</td>
<td>166 ± 9.9</td>
<td>1.97 ± 0.3</td>
<td>7.4 ± 0.5</td>
<td>138 ± 6.3</td>
</tr>
</tbody>
</table>

* Data are given as mean ± SD; n = 8 for each group. P values were obtained by analysis of variance with Scheffé multiple comparison test.

† Data are given as mean ± SD; n = 8 for each group. Degrees of freedom = 2,21. Scheffé multiple comparison test gave P values of <0.0001 to 0.0092 for HBP (20) vs. HBP (R) and SHAM (20) and P values of 0.8811-0.9991 for HBP (R) vs. SHAM (20) for all parameters except RT and DT. This test was not done on data for RT and DT because analysis of variance showed no significant difference between any of the groups of rats for RT or DT.

Previous work (see Discussion for references) indicates that the time course of membrane depolarization can influence the characteristics of the contractile response. Therefore, we reasoned that a rough way to test for a possible physiological relationship between the time course of membrane potential and the nature of the contractile response was to establish whether or not there was a correlation between the time course of the action potential and the parameters that characterize contraction. To accomplish this test with our data, we plotted APD50 and APD75 against four parameters of contraction: peak developed tension (Fig. 2), time-to-peak tension (Fig. 3), time to half relaxation (Fig. 4), and time to peak shortening (Fig. 5). Statistical analysis of these data for SHAM (10) and SHAM (20) muscles showed a significant correlation between all four parameters of contraction and action potential duration. In contrast, HBP (10) muscles showed a significant correlation between only two contractile parameters and action potential duration. Even more striking was the lack of a significant correlation between action potential duration and any

**FIGURE 2.** Relationship between action potential duration and peak developed tension. Values for the correlation coefficient (r) and its corresponding P values are as follows: 2A: ● SHAM (10), r = 0.91, P = <0.01; ○ HBP (10), r = 0.49, P = >0.05; 2B: ● SHAM (10), r = 0.63, P = <0.05; ○ HBP (10), r = 0.48, P = >0.05; 2C: ● SHAM (20), r = 0.72, P = <0.05; ○ HBP (20), r = 0.34, P = >0.05; 2D: ● SHAM (20), r = 0.82, P = <0.01; ○ HBP (20), r = -0.25, P = >0.05; ▲ HBP (R), r = 0.22, P = >0.05.
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FIGURE 3. Relationship between action potential duration and time-to-peak tension (A,C) and time-to-1/2 relaxation (B,D). Values for the correlation coefficient (r) and its corresponding P values are as follows: 3A: • SHAM (10), r = 0.97, P < 0.01; □ HBP (10), r = 0.47, P > 0.05; 3B: • SHAM (10), r = 0.90, P < 0.01; □ HBP (10), r = 0.77, P < 0.05; 3C: • SHAM (10), r = 0.95, P < 0.01; □ HBP (10), r = 0.54, P > 0.05; 3D: • SHAM (10), r = 0.99, P < 0.01; □ HBP (10), r = 0.79, P < 0.01.

FIGURE 4. Relationship between action potential duration and time-to-peak tension (A,C) and time-to-1/2 relaxation (B,D). Values for the correlation coefficient (r) and its corresponding P values are as follows: 4A: • SHAM (20), r = 0.96, P < 0.01; □ HBP (20), r = -0.09, P < 0.01; ▲ HBP (R), r = 0.97, P < 0.01; 4B: • SHAM (20), r = 0.93, P < 0.01; □ HBP (20), r = 0.43, P > 0.05; ▲ HBP (R), r = 0.85, P < 0.01; 4C: • SHAM (20), r = 0.63, P < 0.05; □ HBP (20), r = 0.35, P > 0.05; ▲ HBP (R), r = 0.53, P > 0.05; 4D: • SHAM (20), r = 0.75, P < 0.05; □ HBP (20), r = 0.52, P > 0.05; ▲ HBP (R), r = 0.27, P > 0.05.

FIGURE 5. Relationship between action potential duration and time-to-peak shortening. Values for the correlation coefficient (r) and its corresponding P values are as follows: 5A: • SHAM (10), r = 0.82, P < 0.02; □ HBP (10), r = 0.74, P > 0.05; ▲ HBP (R), r = 0.70, P > 0.05; 5B: • SHAM (10), r = 0.74, P < 0.05; □ HBP (10), r = 0.74, P > 0.05; ▲ HBP (R), r = 0.70, P > 0.05; 5C: • SHAM (20), r = 0.79, P < 0.05; □ HBP (20), r = 0.58, P > 0.05; ▲ HBP (R), r = 0.07, P > 0.05.

of the four contractile parameters in HBP (20) muscles. In view of this last observation, it is remarkable that in HBP (R) preparations a significant correlation was restored between action potential duration and three of the four contractile parameters.

Discussion

Previous work on experimental hypertrophy indicates that the mechanical and electrical alterations associated with this process vary according to the animal species, the method used to induce hypertrophy, and the duration of the pressure load prior to study (Spann et al., 1967; Bing et al., 1971; Spann et al., 1972; Meerson and Kapelko, 1972; Bassett and Gelband, 1973; Gelband and Bassett, 1973; Jouannot and Hatt, 1975; Bing et al., 1978; Capasso et al., 1981). On the other hand, certain important features of the hypertrophy process emerge from prior studies and our own. In rats and rabbits (Hamrell and Alpert, 1977) with hypertrophy produced by pressure overload, most studies report normal or increased developed tension, decreased velocity of shortening, increased time-to-peak tension, and increased time-to-peak shortening. In rats with hypertrophy induced by renal hypertension, this constellation of mechanical properties is invariably associated with prolonged action potentials (Aronson, 1980). In contrast, in cats with chronic right ventricular hypertrophy, developed tension is reduced and the velocity of shortening and maximum rate of tension development are decreased.
The mechanical alterations associated with this model of right ventricular hypertrophy in the cat occurred without changes in the action potential in the absence of heart failure (Bassett and Gelband, 1973), whereas with heart failure the action potential was depressed and lasted longer (Gelband and Bassett, 1973).

Our results suggest that the longer duration of contraction in rats with left ventricular hypertrophy may be related to the longer action potential duration observed in hypertrophied muscle. This view is based on previous studies showing that the nature of the contractile response can be influenced by the time course of membrane depolarization (Kavaler, 1959; Morad and Trautwein, 1968; Wood et al., 1969; Kavaler et al., 1972; Edman and Johannsson, 1976; Allen, 1977; Beresewiez and Reuter, 1977). However, the nature of the relationship between contraction and membrane depolarization is far from clear and may vary according to both species and experimental conditions. For example, the duration of membrane depolarization could influence contraction by regulating the release and uptake of calcium from the sarcoplasmic reticulum (Fozzard, 1977; Fabiato and Fabiato, 1979). Such regulation could occur by longer lasting depolarizations causing depolarization of more total area of T-system membrane. Release of calcium from the sarcoplasmic reticulum would then occur in proportion to the duration of adjacent depolarized T-system membrane. Removal of depolarization then would trigger uptake of calcium by adjacent sarcoplasmic reticulum and thereby start relaxation via the activity of the calcium transport system.

The results of this study suggest that the time course of contraction and the magnitude of developed tension are strongly interrelated, at least in normal rat papillary muscles. This view is supported by both the strong positive correlation between action potential duration and various parameters of the contractile response in SHAM (10) and SHAM (20) rats, we and similar studies done in rabbit myocardium (Wolfhart, 1979) observed and by a voltage-clamp study (Leoty, 1974) that showed that the level of maximum contraction was steeply dependent on the clamp pulse duration, especially for durations <100 msec. As the duration of the depolarizing clamp pulses was made longer than 100 msec the dependence of the magnitude of contractile force on the duration of depolarization was much less steep.

If this analysis is valid, then it seems reasonable to suggest that the long action potentials associated with LVH in rats may be an important factor in prolonging the duration of contraction. According to this view, the longer duration of depolarization somehow prolongs the duration of contraction to a sufficient degree to maintain normal levels of developed tension despite reduced shortening velocity and rate of tension development. Since the maximum tension development in rat ventricular muscle is affected very little by depolarizations lasting > 100 msec (Leoty, 1974), it is possible that once the duration of the action potential reaches a certain length, further lengthening of the action potential does not influence tension development. This could account for the disappearance of the good correlation between action potential duration and parameters of contraction in HBP muscles as well as for the restoration of this correlation in HBP muscles.

On the other hand, it is possible that the long action potentials observed in left ventricular hypertrophy are secondary to the alterations in contraction. For example, Kaufmann, et al. (1971) suggested that the duration of the action potential can be influenced by the mode of contraction in cat papillary muscle. These investigators reported that isotonic shortening tends to prolong, whereas isometric tension development tends to shorten the APD. Our results also show that APD is influenced by the mode of contraction in both SHAM and HBP papillary muscles. However, in contrast to Kaufmann et al. (1974), our data in the rat show that isotonic shortening is associated with shorter action potentials than isometric tension development. In any case, the degree of change in APD associated with entirely different modes of contraction is much smaller than that seen between normal and hypertrophied myocardium.

The fact that the mechanical and electrical alterations associated with left ventricular hypertrophy reverse almost completely and in parallel has some interesting implications. It suggests that the contractile apparatus and the surface membrane are not irreversibly altered, even after 10 weeks of pressure overload. It also suggests that the lengthening of the duration of contraction and the action potential are functionally related compensatory adaptations to pressure overload on the heart. In addition, it supports the view that up to a point that has yet to be defined, cardiac hypertrophy is truly adaptive rather than a pathological process.

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