Non-uniform Electrophysiological Properties and Electrotonic Interaction in Hypertrophied Rat Myocardium

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SUMMARY We studied the distribution and nature of the electrical changes associated with myocardial hypertrophy induced by renal hypertension in rats. Standard microelectrode techniques were used to study transmembrane action potentials recorded from endocardial, papillary muscle, and epicardial fibers from hypertrophied (HBP) and normal (SHAM) hearts. We also determined the effects of stimulation frequency on the action potentials recorded from these preparations. To assess whether altered intercellular electrical connections contribute to the electrophysiological changes associated with hypertrophy, we analyzed the spatial steady state voltage decrement produced by passing intracellular constant current pulses and determined the effective input resistance ($R_i$) of endocardial HBP and SHAM preparations. Our results show that the action potential prolongation that accompanies hypertrophy is not uniform. Thus, the entire course of repolarization is prolonged in endocardial and papillary muscle fibers, but only the latter half of repolarization is prolonged in epicardial fibers. Endocardial action potentials in general, and HBP action potentials in particular, have a distinctive steep relation between duration and stimulation frequency which may be due to a difference in the rate dependence of a membrane conductance(s), although relatively greater accumulation of extracellular potassium or altered activity of the Na$^+-$K$^+$ pump cannot be excluded as contributing factors. In addition, the similarity in the profile of spatial voltage decrement and the values for $R_i$ in HBP and SHAM preparations indicates that alterations in electrotonic coupling between cells are unlikely to account for the prolonged action potentials of hypertrophied myocardium. Circ Res 49: 150–158, 1981

RENOVASCULAR hypertension in rats produced by unilateral clipping of one renal artery imposes a gradual and chronic pressure overload on the heart. Left ventricular hypertrophy resulting from such a chronic pressure overload is associated with characteristic contractile (Jacob et al., 1977; Kammereit and Jacob, 1979; Capasso et al., 1980), ultrastructural (Wendt-Gallitelli and Jacob, 1977; Loud et al., 1978; Anversa et al., 1978; Wendt-Gallitelli et al., 1979), and electrophysiological alterations (Gulch et al., 1979; Aronson, 1980).

The most consistent alterations in the myocardium of rats with renal hypertension are enlargement of the myocytes and prolongation of the action potential. However, the degree of alteration in these properties appears to vary according to the region of the left ventricle studied. For example, in a morphometric study of hypertrophied left ventricles from rats with renal hypertension, Loud et al. (1978) and Anversa et al. (1978) reported a greater enlargement of epicardial cells than endocardial cells after 1–4 weeks of hypertension. In the same model, Aronson (1980) recently reported a 50% prolongation of action potential duration in hypertrophied rat papillary muscle driven at a cycle length of 1000 msec (35°C), and Gulch et al. (1979) reported a 180% increase in action potential duration in left ventricular trabeculae driven at a cycle length of 5000 msec (25°C). These results suggest that hypertrophy induced by renal hypertension may be a non-uniform process that affects endocardial, papillary muscle, and epicardial fibers to a different degree.

The purpose of the present study was to characterize further the distribution and nature of the electrical changes associated with myocardial hypertrophy. This was done by studying the action potentials recorded from epicardial, papillary muscle, and endocardial fibers, by determining the effects of stimulation frequency on action potentials recorded from these sites, and by comparing passive membrane properties by analysis of the profile of electrotonic voltage decrement.

Methods

Experimental Procedures

Experimental male Wistar rats weighing 160–180 g were made hypertensive by the placement of a silver clip (0.22-mm aperture) around the left renal artery. Age-matched rats were subjected to a sham operation which was identical to that used in ex-
peripheral rats except that no clip was placed around the left renal artery. Systolic blood pressure was taken under light ether anesthesia by the tail cuff microphonics manometer method at 2-week intervals after operation. Studies were performed 8 weeks after clipped animals had developed hypertension (systolic blood pressure \( \geq 170 \) mm Hg). Under ether anesthesia, hearts were removed from hypertensive (HBP) and age-matched sham-operated (SHAM) rats. The hearts were submerged in Tyrode's solution at room temperature and three kinds of tissue preparations were obtained from the left ventricle of each heart: (1) papillary muscles, (2) endocardial preparations measuring 2-3 mm \( \times \) 5 mm \( \times \) 1 mm (thickness) and (3) epicardial preparations of the same dimensions as endocardial preparations. Endocardial and epicardial preparations were obtained by carefully undercutting the corresponding surface of the ventricle with a curved scissors. Papillary muscle, endocardial, and epicardial preparations from each heart were mounted in a tissue bath perfused with Tyrode's solution at 35\(^\circ\)C and having the following composition in mM/liter: \( \text{Ca}^{2+}, 2.4; \text{Na}^+, 137.5; \text{Mg}^{2+}, 0.5; \text{K}^+, 4.0; \text{Cl}^-, 147.3; \text{H}_{2}\text{PO}_4^-, 1.8; \text{HCO}_3^-, 12.0; \text{glucose}, 5.5. \)

**Transmembrane Action Potentials**

Preparations were driven regularly at a cycle length of 1000 msec and were allowed to equilibrate for at least 1 hour before the first recordings were taken. Transmembrane action potentials were recorded by standard microelectrode techniques from HBP and SHAM muscle preparations. External stimuli were delivered to the tissue through bipolar Teflon-coated silver wires. The timing of the stimulating pulses was regulated by a digital timing system interfaced with a pulse generator connected to a stimulus isolation unit. Photographic records were obtained with a Polaroid oscilloscopic camera (Tektronix C5A).

To determine the effects of increasing stimulation frequency, preparations were driven at 5 cycle lengths. The drive cycle length (DCL) was decreased every 90 seconds from 1000 to 600, 300, 200, and 150 msec and then was restored to 1000 msec. We found that 90 seconds were sufficient for action potential duration to reach a steady state at each successive decrease in DCL. However, when the DCL was restored to 1000 msec, it took 3-5 minutes for the action potential duration to reach a new steady state. Measurements were made only from records obtained from experiments in which one impalement was maintained in the same cell during the entire sequence of DCL changes. Three such maintained impalements were made in each type of preparation (endocardial, epicardial, and papillary muscle). Therefore, each measured action potential parameter is reported as the mean value of three impalements maintained at random sites in each preparation.

**Analysis of Electronic Voltage Decrement**

To investigate the role of alterations in intercellular electrical coupling in prolonging action potential duration in endocardial HBP preparations, we studied the profile of spatial decrement of the electrotonic voltage deflection produced by injecting a constant current pulse. We initially attempted to do this analysis in trabeculae 2-4 mm in length by injecting a current pulse through one microelectrode while measuring the resulting voltage decrement with a second microelectrode. In such preparations we found that the voltage decrement with distance was so steep that it precluded doing a reliable comparative analysis of the spatial decrement of electrotonic potential in HBP and SHAM preparations. That is, the voltage dropped off so steeply that measurements would have to be obtained within a total distance of less than 0.2 mm. The much steeper than exponential decay of electrotonic potential clearly indicated that current flow in these preparations was multidimensional (Woodbury and Crill, 1961; Sakamoto, 1969).

Since it is known that the decrement of voltage is very much smaller in one-dimensional finite than infinite cables (Jack et al., 1975), we reasoned that the extremely steep voltage decrement seen in our multidimensional trabecular preparations might be decreased sufficiently in short preparations to allow us to analyze differences in the passive membrane properties of HBP and SHAM preparations. Although we are not aware of a theoretical equation that can be used to calculate the voltage decrement expected in a finite multidimensional preparation, we assumed that a direct comparison of the profile of voltage decrement in HBP and SHAM preparations would at least permit us to identify a difference in those passive membrane properties that determine the pattern of current flow. To obtain a rough estimate of what a reasonable length of preparations should be for our experiments, we first determined the length constant, \( \lambda \), of normal rat ventricular muscle by one-dimensional cable analysis (Kamiyama and Maizada, 1966; Tille, 1966; Sakamoto and Goto, 1970). In four ventricular muscle preparations \( \lambda \) was 1.0 \pm 0.2 mm (mean \pm s.d.), a value similar to that reported in a previous study (Mainwood and McGuigan, 1975).

Accordingly, our subsequent experimental procedure was as follows. Trabeculae measuring 2-4 mm in length and 0.5-1.0 mm in diameter were removed from the endocardial surface of the left ventricular free wall of four HBP and four SHAM rats. These preparations were mounted in a tissue bath previously described (Aronson et al., 1973) but modified so that the distance between the wires crushing the preparations was 0.7 mm. This bath produced two to four electrically isolated tissue segments from each trabecula. Hyperpolarizing constant current pulses (\( I_a = 0.6 \mu A \)) lasting 120 msec were injected at 2-second intervals via an intracel-...
lular glass microelectrode positioned near one end of the tissue segment. By placing the current passing electrode as close as possible to one end of the tissue segment, the effective electrotonic current can be theoretically increased 2-fold (Jack et al., 1975). The electrotonic voltage deflection produced by the current pulse was recorded by a second electrode positioned at various axial distances along each isolated segment. As has been reported for other preparations in which current spread is multidimensional (Woodbury and Crill, 1961; Tanaka and Sasaki, 1966), we found that the decay of voltage was much steeper in the direction perpendicular to the fiber bundles than parallel to the bundles. Therefore, in all of our experiments, we paid careful attention to keeping the voltage recording electrode and the current passing electrode in a co-linear relation to the axial direction of the fiber bundles.

The following parameters were measured:

- \( V_0 \) = the steady state voltage deflection recorded when the voltage recording electrode was at a distance \( x = 0 \) mm from the current-passing electrode.
- \( x \) = the distance in mm between the current-passing and voltage-recording electrodes.
- \( V \) = the steady state voltage recorded at various values of \( x \).

### Spatial Voltage Decrement Calculation

The profile of spatial voltage decrement was obtained by plotting \( V/V_0 \) against \( x \) and 

\[
V/V_0 = \left( \frac{V}{V_0} \right) = \exp \left( -\frac{x}{\lambda} \right)
\]

where \( \lambda = 1.0 \) mm. The profile of spatial voltage decrement for the two-dimensional case was calculated according to the following equation (Tanaka and Sasaki, 1966):

\[
V/V_0 = \frac{1}{m} K_0(x/\lambda)
\]

where \( m = 4.50 \) for \( \lambda = 1.0 \) mm and assuming that the muscle fibers anastomose at intervals of 100 \( \mu \)m. \( K_0 \) is a zero order modified Bessel function of the second kind.

### Data Analysis

The statistical significance of differences in systolic blood pressure, heart weight, body weight, and heart weight to body weight ratio, were assessed by Student's t-test for unpaired data.

The data analysis employs the variance ratio, F, to determine significance. A sufficiently high F value indicates that a statistically significant difference exists between the variables being compared. F values were determined for: (1) group differences (SHAM vs. HBP) and (2) site differences that are independent of recording site and DCL and (3) interaction between group and DCL that are independent of DCL and (4) interaction between site and DCL that are independent of group and DCL.

In a factorial experiment such as ours, several factors, i.e., animal group, recording site, and DCL, are investigated simultaneously (Winer, 1971). In analyzing this kind of experiment, different designated categories of the factors are called levels. For example, there are two levels in the group factor, namely, HBP and SHAM and three levels in the site factors, namely, endocardial, epicardial, and papillary muscle. This kind of experimental design also permits identification of interactions between factors. Accordingly, we analyzed our data for: (1) interaction between group and DCL that are independent of site and (2) interaction between site and DCL that are independent of group. Interaction between two factors (e.g., group and DCL) is present when a change in one factor (DCL) produces a change in response (APD) at one level of the other.
factor (HBP) different from that produced at the other level of this factor. In other words, there is interaction between group and DCL for action potential duration because decreasing DCL produces a greater shortening of HBP action potential duration than SHAM action potential duration (see Fig. 4). The mean scores for each action potential duration are used in Figures 4 and 5. The definition of the mean score is best presented by the following example. The mean score for APD_{25} in the HBP group is the sum of the mean values of APD_{25} from all three sites for seven HBP animals divided by the product of the number of sites (3) and the number of observations per site (7). Single-degree of freedom contrast was used to test the significance of the difference in action potential duration of HBP vs. SHAM fibers at each DCL.

### Results

The characteristics of the animal groups used in our studies are shown in Table 1. These data show that systolic blood pressure and heart weight were significantly greater in HBP rats but that there was no significant difference in body weight between animal groups. The mean heart weight of HBP rats was increased by 33%.

Typical action potentials recorded at three DCL are shown in Figure 1. These records show that, in general, both HBP and SHAM action potentials shorten as the DCL is increased. However, as illustrated in Figure 2, the degree of shortening and the relative change in action potential contour vary according to the recording site and animal group. The data in Figure 2 show that endocardial and papillary muscle HBP action potentials were consistently longer than SHAM action potentials at all DCL but that epicardial HBP action potentials were similar to epicardial SHAM action potentials, except for APD_{75}.

Statistical analysis of the data in Figure 2 is presented in Figure 3 where F values for APD_{25}, APD_{50}, and APD_{75} of HBP vs. SHAM preparations at each recording site are plotted against DCL. On the one hand, APD_{25}, APD_{50}, and APD_{75} of endocardial and papillary muscle preparations were significantly ($P < 0.05$) longer for HBP than SHAM action potentials at all DCL. On the other hand, APD_{25} and APD_{50} of epicardial action potentials were not significantly longer for HBP than SHAM preparations ($P > 0.05$) at any DCL. However, APD_{75} of epicardial action potentials was significantly longer ($P < 0.05$) for HBP than SHAM preparations at all DCL except 150 msec. These results suggest that the prolongation of HBP action potentials is more marked in endocardial and papillary muscle fibers than in epicardial fibers and that the prolongation of the latter half of repolarization (APD_{50}) of epicardial HBP action potentials is diminished by decreasing the DCL.

In addition to the absolute differences in duration between HBP and SHAM action potentials discussed above, Figure 2 shows that the response of action potential duration to decreasing DCL is different, according to animal group and recording site. To establish that these differences are quantitatively significant, the patterns of response of action potential duration to decreasing DCL were analyzed further.

The results of this analysis showed that the ac-

### Table 1 Characteristics of Animal Group

<table>
<thead>
<tr>
<th></th>
<th>Systolic blood pressure (mm Hg)</th>
<th>Heart weight (g)</th>
<th>Body weight (g)</th>
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<tbody>
<tr>
<td>SHAM (n = 11)</td>
<td>141 ± 12</td>
<td>0.93 ± 0.15</td>
<td>492.4 ± 64.3</td>
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<tr>
<td></td>
<td>$P &lt; 0.001$</td>
<td>$P &gt; 0.005$</td>
<td>$P &gt; 0.05$</td>
</tr>
<tr>
<td>HBP (n = 11)</td>
<td>215 ± 23</td>
<td>1.24 ± 0.16</td>
<td>478.1 ± 47.5</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD. n = number of rats.
Effects of DCL on the action potential duration of endocardial (○), epicardial (●), and papillary muscle (△) action potentials of HBP (filled symbols) and SHAM (unfilled symbols) rats. Values are presented as mean ± SD, n = 7. A small dot is used to mark the bars representing SD for papillary muscles.

Figure 6 shows the mean values for amplitude and resting membrane potential at various DCL. Statistical analysis of this data showed that: (1) amplitude was significantly (P < 0.001) lower in epicardial than in papillary muscle and endocardial action potentials in both HBP and SHAM fibers but was not significantly (P > 0.05) different between animal groups; (2) resting membrane potential was not significantly different between recording sites (P > 0.05) or between animal groups (P > 0.05); (3) both amplitude and resting membrane potential decreased significantly (P < 0.001) as a function of decreasing DCL, but the pattern of decrease was not significantly different between either animal group (P > 0.05) or recording site (P > 0.05).

Figure 7 shows the profile of steady state voltage decrement of endocardial trabecular preparations as a function of the distance between the current-passing and voltage-recording electrodes. All but one of the experimental points obtained for both HBP and SHAM preparations fall below the theoretical curve representing the profile of voltage decay expected for a one-dimensional infinite cable. Although all the experimental points lie above the theoretical curve for an infinite two-dimensional model, the shape of the curve is strongly dependent upon the value of λ. Increasing the value of λ would produce a curve that more closely fits the experimental data. The profile of voltage decay is similar for HBP and SHAM preparations. R∞ of HBP (60.5 ± 26.4 kΩ, n = 4) and SHAM (64.7 ± 15.9 kΩ, n = 4) preparations was not significantly different (P > 0.05).

Figure 3 Statistical significance of differences in APD for SHAM vs. HBP fibers at each DCL. Symbols for recording sites: endocardial (○), epicardial (●), and papillary muscle (△) fibers. F values are plotted on the ordinate against DCL on the abscissa. Degrees of freedom = 1, 36. Probability levels are indicated to permit assessment of statistical significance.
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Figure 4 Relation between group and DCL independent of recording site. Symbols for groups: HBP (●) and SHAM (○). APD₂₅, APD₆₀, and APD₉₀ are expressed as mean scores for records from endocardial, epicardial, and papillary muscle preparation for each group for each DCL. n = number of sites (3) × number of observations per site (7). There is no significant difference between the action potential duration-DCL curves for APD₂₅, but there is a highly significant difference between the curves of HBP and SHAM preparations for APD₆₀ (P < 0.05) and APD₉₀ (P < 0.001). Therefore, a significant group-DCL interaction is present and is due to the much steeper relation between APD and DCL in HBP fibers.

Discussion

Our results show that hypertrophied myocardium of rats with renal hypertension has a distinctive distribution of action potential duration according to recording site (Fig. 2). HBP epicardial action potentials are significantly shorter during the first half of repolarization than those of either papillary muscle or endocardial action potentials. A similar disparity in action potential duration between epicardial and papillary muscle and endocardial fibers has been reported in previous studies in normal canine (Gilmour and Zipes, 1980), rabbit (Fukushima, 1970), and sheep (Cohen et al., 1976) ventricular fibers.

In addition, our data show that, whereas the entire course of repolarization is significantly longer than 0.10); data are presented as mean ± sd, number of preparations.

Figure 5 Relation between recording site and DCL independent of group. Symbols for recording sites: endocardial (●), epicardial (▲), and papillary muscle (○). APD₂₅, APD₆₀, and APD₉₀ are expressed as mean scores for records from HBP and SHAM preparations for each site for each DCL. n = number of groups (2) × number of observations per group (7). There is a significant difference between the action potential duration-DCL curves of endocardial as compared to those of epicardial and papillary muscle fibers for APD₂₅ (P < 0.001), APD₆₀ (P < 0.001), and APD₉₀ (P < 0.01). Therefore, a significant site-DCL interaction is present and is the result of the steeper action potential duration-DCL relation of endocardial fibers.

Figure 6 Effects of DCL on amplitude and resting membrane potential of endocardial, epicardial, and papillary muscle action potentials from HBP and SHAM rats. Symbols are the same as in Figure 2. The data are presented as mean values ± sd, n = 7.
in endocardial and papillary muscle action potentials of HBP than SHAM fibers, epicardial action potentials are similar in duration in HBP and SHAM fibers during the first half of repolarization (Fig. 3). However, during the latter half of repolarization, epicardial action potentials are again longer in HBP than SHAM fibers (Fig. 3). Thus, our data indicate that the latter half of repolarization is prolonged selectively in epicardial cells in contrast to the overall lengthening of repolarization in endocardial and papillary muscle fibers.

The relatively shorter duration of epicardial action potentials also was reported recently by Gulch (1980), who found that the half-width duration of action potentials of endocardial fibers was longer than that of epicardial fibers in hypertrophied myocardium from rats with renal hypertension. However, the measurement of action potential duration by half-width only might falsely exaggerate the difference in duration between endocardial and epicardial action potentials, since we report here that epicardial fibers have a selective prolongation of only the latter half of repolarization.

Previous studies of the electrophysiological effects of cardiac hypertrophy involving the right ventricle of cats have reported no significant change in action potential parameters (Kaufmann et al., 1971), transient depression of the plateau phase 3–10 days after induction of hypertrophy (Bassett and Gelband, 1979), and prolongation of action potential duration (Trithart et al., 1975; Ten Eick et al., 1977, 1978). In cats showing evidence of congestive heart failure, the action potentials showed marked alterations (Gelband and Bassett, 1973). In contrast to the variable electrophysiological changes observed in cats with right ventricular hypertrophy, we (Aronson, 1980) and others (Gulch et al., 1979) have found substantial and consistent prolongation of action potentials in rats with left ventricular hypertrophy induced by renal hypertension. In addition, it has been reported that spontaneously hypertensive rats (Hayashi and Shibata, 1974; Heller and Stauffer, 1979) and rats made hypertensive with deoxycorticosterone acetate (Heller and Stauffer, 1979) have longer action potentials than do control rats. To our knowledge, there is only one previous study addressing the question of uniformity of the electrophysiological changes associated with hypertrophy (Gulch, 1980) and no previous studies of the electrophysiological response of hypertrophied myocardium to increasing stimulation frequency.

A relation between action potential duration and cell-to-cell electrical coupling is suggested by both the syncitial structure of cardiac muscle (Johnson and Sommer, 1967) and a recent study by Wojtczak (1979). The latter study reported that an increase in the internal longitudinal resistance of cell-to-cell electrical connections is temporally correlated with a shortening of the action potential during hypoxia. Our analysis of the passive current spread in endocardial HBP and SHAM preparations does not support the hypothesis that an alteration in intercellular electrical coupling is responsible for lengthening of HBP action potentials. Our finding that the profile of voltage decrement in both HBP and SHAM preparations was steeper than that expected for an infinite one-dimensional cable supports the view that current flow is multidimensional. It has been shown that, in multidimensional models, for a small separation between current-passing and -recording electrodes, $R_m$ is relatively insensitive to membrane resistance and thus is mainly a function of internal longitudinal resistance (Berkinblit et al., 1971; Jack et al., 1975). Therefore, in our preparations, any alterations detected in the pattern of voltage decrement would be more strongly dependent on the internal longitudinal than the membrane resistance. We found that values of $R_m$ of HBP and SHAM preparations were not significantly different and that there was a lack of any consistent difference in the profile of voltage decrement between HBP and SHAM preparations (Fig. 7). These results support the view that elec-
metrical couplings between cells are functionally similar in HBP and SHAM preparations and, therefore, alterations in electrotonic coupling are unlikely to account for action potential prolongation in hypertrophied myocardium.

Another interesting result was that endocardial fibers in general and HBP fibers in particular demonstrate a characteristic physiological response to increasing stimulation frequency. This is reflected by the findings that endocardial fibers of either HBP or SHAM myocardium have a much steeper action potential duration-DCL relation than papillary muscle or epicardial fibers (Fig. 5) and that HBP fibers have a significantly steeper action potential duration-DCL relation than SHAM fibers (Fig. 4). Thus, the action potentials of HBP fibers resemble those of endocardial fibers in that both demonstrate a quantitatively greater degree of shortening in response to increasing stimulation frequency. In contrast to duration, resting membrane potential and amplitude both decrease as stimulation frequency is increased, but the degree of decrease is not significantly different with respect to either recording site or animal group (Fig. 6).

Possible mechanisms for the greater sensitivity of endocardial action potentials, especially HBP, to increasing stimulation frequency include slower deactivation kinetics of an outward current, slower reactivation kinetics of an inward current, greater accumulation of K⁺ in extracellular space, and augmented electrogenic repolarizing current generated by enhanced activity of Na⁺-K⁺ pump (Carmeliet, 1977; Gadsby and Cranefield, 1979). The finding that resting membrane potential and amplitude show a similar pattern of decline with increasing frequency of stimulation at all recording sites in both animal groups suggests that the degree of extracellular K⁺ accumulation is similar and, thus, may not be primarily responsible for the differentially greater shortening of endocardial action potentials. Similarly, one might suppose that an increase in Na⁺-K⁺ pump activity sufficient to produce a substantial degree of shortening of action potential duration would also differentially reduce the degree of decline in resting membrane potential and amplitude of endocardial fibers as the drive rate was increased. Since this was not observed in our experiments, enhanced Na⁺-K⁺ pump activity may not be primarily responsible for the greater shortening of endocardial action potentials with increasing drive rate. Furthermore, recent evidence indicates that the outward currents responsible for repolarization in ventricular muscle are relatively insensitive to increased extracellular K⁺, at least in the cat (McDonald and Trautwein, 1978).

The indirect evidence presented above cannot, of course, exclude the possibility that K⁺ accumulation, either by a direct or indirect action, or altered Na⁺-K⁺ pump activity could account at least in part for the greater sensitivity of action potential duration to DCL changes in HBP and endocardial fibers.

For example, an outwardly rectifying K⁺ channel could be sensitive to K⁺ only at depolarized levels of membrane potential, and such an effect would not be detected by changes in resting membrane potential or action potential amplitude. Furthermore, it has been shown recently by Gadsby and Cranefield (1979) that "small changes in pump activity can markedly affect the duration of the action potential in cardiac Purkinje fibers." It is possible that enhanced pump activity induced by increased stimulation frequency could influence the membrane potential during the course of repolarization without necessarily affecting either the resting membrane potential or action potential amplitude. For example, enhanced electrogenic pump activity might influence the membrane potential during repolarization when the membrane resistance is relatively high but have little effect on the resting membrane potential during diastole when the membrane resistance is relatively low.

Available evidence indicates that the duration of ventricular action potentials is much more strongly dependent on inactivation of the slow inward current (iₙ) than on activation of outward K current (iₖ) (Beeler and Reuter, 1977; Carmeliet, 1977). This suggests that the greater degree of rate-dependent shortening of endocardial action potentials may be due to a rate-dependent alteration in iₙ, as opposed to an alteration in iₖ.

An important general implication of our results is that the electrophysiological behavior of one part of the ventricle cannot be assumed to apply in other parts, a point that has been made previously by others (Cohen et al., 1976). For example, Blesa et al. (1970) reported that there was no change in the duration of right ventricular papillary muscle action potentials of the rat when stimulation rate was increased. Although the duration of papillary muscle and epicardial action potentials show little change as drive rate increases (Fig. 4), this is clearly not the case for endocardial action potentials. Therefore, the behavior of papillary muscle action potentials cannot be taken to be representative of that of other parts of the rat myocardium.

In summary, our results show that the action potential prolongation that accompanies hypertrophy in rats is not uniform. Thus, the entire course of repolarization is prolonged in endocardial and papillary muscle fibers but only the latter half of repolarization is prolonged in epicardial fibers. Endocardial action potentials in general, and action potentials of hypertrophied muscle in particular, have a distinctive steep relation between duration and drive rate which may be due to a difference in the rate dependence of a membrane conductance(s), although relatively greater accumulation of extracellular K⁺ or altered activity of the Na⁺-K⁺ pump cannot be excluded as contributing factors. Finally, the similarity in the profile of spatial voltage decrement and the values for R₀ in HBP and SHAM preparations suggests that alterations in electro-
tonic coupling between cells probably does not account for the prolonged action potentials of hypertrophied myocardium.

Acknowledgments

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