Depressed Transmembrane Potentials during Experimentally Induced Ventricular Failure in Cats

By Henry Gelbond and Arthur L. Bassett

ABSTRACT

Transmembrane potentials and isometric force were recorded in right ventricular muscles from cats with right ventricular failure 3–127 days after chronic partial pulmonary artery obstruction. For the majority of failed muscles (at 36°C, 30 stimuli/min), resting potential, action potential overshoot, action potential maximum rate of rise, isometric active force at optimal length ($P_o$), and $dP/dt$ were decreased compared with the same parameters in normal muscles. Time to peak force and duration of contraction were unaltered. Action potential configuration was changed and action potential duration was lengthened in failed muscles. Epinephrine ($10^{-5} M$) markedly increased $P_o$ and resting potential in severely depolarized failed muscles. These data suggest that electrical depression might exacerbate the contractile deficit in experimental chronic right ventricular failure.

KEY WORDS

cardiac muscle
ventricular systolic hypertension
epinephrine
congestive heart failure
microelectrode techniques
elevated ventricular end-diastolic pressure
isometric force
resting potential
action potential amplitude

Methods

Right ventricular muscles were obtained from normal cats and cats with overt right ventricular failure induced by chronic partial constriction of the main pulmonary artery. Adult cats (1.5–2.4 kg) were anesthetized with sodium pentobarbital (30 mg/kg, ip), and an electrocardiogram was recorded on a multichannel oscillograph (Electronics for Medicine).
Respiration was maintained with intermittent endotra- cheal positive pressure. The main pulmonary artery was constricted with umbilical tape to approximately 10–20% of its original measured diameter. Seven cats were subjected to an identical operation except that a loose nonocclusive tie was placed around the pulmonary artery; these cats were designated sham-operated cats. After the surgical procedure (3–127 days), the cats were weighed and anesthetized with sodium pentobarbital (30 mg/kg, ip), and an electrocardiogram was recorded. After tracheostomy, each cat was ventilated with intermittent positive pressure. The chest was opened, and right ventricular pressure was measured by direct puncture of the ventricular cavity with a 22-gauge needle attached to a flexible catheter and a Statham blood pressure transducer; pressure was recorded on the oscillograph. Cats were considered to be in right ventricular failure when right ventricular end-diastolic pressure was markedly elevated (> 8 mm Hg) in combination with two or more of the following physical signs: ascites, pleural effusion, or hepatomegally.

After ventricular pressure had been measured, the heart was rapidly excised and washed in several changes of Tyrodes solution at room temperature. Tyrode’s solution was equilibrated with 95% O2-5% CO2 and had the following millimolar composition: NaCl 137, NaHCO3 12, KCl 4, CaCl2 2.7, NaH2PO4 1.8, MgCl2 0.5, and dextrose 5.5. A papillary muscle was dissected from the free wall of the right ventricle and was mounted horizontally in a water-jacketed Lucite myograph with a chamber volume of 8 ml. Chamber temperature was maintained at 36±0.1°C by admitting warmed Tyrode’s solution to the chamber at a rate of 6 ml/min and by heating the water flowing through the external jacket (3). The heating and infusion systems were arranged so that, when inflow of Tyrode’s solution to the muscle chamber was shut off, both the level and the temperature of the solution in the chamber were maintained constant. This procedure permitted the addition of drugs directly to the chamber under controlled conditions. Uniform distribution of the drug throughout the chamber resulted from the mixing action of the 95% O2-5% CO2 bubbled into the chamber through a fine sintered glass dispersion tube.

Force was measured for each muscle with a Statham UC2 transducer mounted horizontally through one wall of the myograph; the output of the transducer was amplified and displayed along with the first derivative of force on the oscillograph and often on an oscilloscope (3). Muscle length was set to give a small resting force by adjusting a fine micrometer movement at the opposite end of the myograph, and stimulation was initiated. Muscle length was then gently adjusted to optimal length so that each muscle developed its maximal isometric active force (P0) at the temperature, the rate of stimulation, and the ionic environment used in this study. Resting force was also determined for each preparation at optimal length.

Muscle cross-sectional area at optimal length was determined as previously described (3). Active and resting force and the maximum rate of development of force were expressed per cross-sectional area. We selected muscles of reasonably similar cross-sectional areas from the three groups of cats to simplify analysis of the mechanical properties.

After the muscle preparation was obtained, the atria and the blood vessels were dissected from the heart. Surface fat was trimmed from the ventricles, and the right ventricular free wall was dissected free and weighed after gentle blotting to remove surface water; the same procedures were used for the left ventricle and septum. The free wall of the right ventricle was dried to a constant weight at 100°C over 1–2 days. Ventricular weights are expressed relative to body weight at the time of study. Body weight for the cats subjected to surgery did not differ significantly from the preoperative weight. In most instances, however, there was a slight loss of body tissue weight, since the pleural and the ascitic fluid in cats with right ventricular failure represented part (less than 10%) of the total body weight. This assumption about body tissue weight neglects the possibility that intracellular water is increased during heart failure (4).

The muscles were stimulated through fine bipolar silver wires insulated with Teflon except at the tips. In several experiments, we used high-intensity field stimulation (5) applied via close silver wires positioned parallel to the long axis of the muscle. For either mode of stimulation, the pacing rate was set at 30/m with square-wave pulses 2-3 msec in duration. Stimulation voltage was set 5–10% above threshold. Intracellular recordings were obtained with glass microelectrodes and electronic circuitry (3). The outputs of the microelectrode preamplifier and the transducer amplifiers were displayed on a dual-beam or a storage oscilloscope (Tektronix RM565 or RM564) and were photographed with Polaroid or Grass Instrument cameras. Input capacity neutralization and the maximum rate of rise of phase 0 of the action potential were monitored on each sweep of the oscilloscope (6). For each muscle, numerous impalements of cells were made across the surface and down several layers to sample the population of cells. The data reported in Table 3 resulted from measurements of electrical properties in 10–20 individual cells for each muscle. For the figures, we selected a recording which was representative of the action potential configuration of the population of cells in the particular muscle. Although action potential configuration varied from muscle to muscle, within any given muscle the action potential configuration was qualitatively similar from cell to cell. Most measurements of electrical and mechanical properties were made 1–1½ hours after the muscle was placed in the chamber, although in some experiments we began to monitor transmembrane potentials and force within 10 minutes. Action potential duration was measured at 70% and 100% repolarization. Duration of phase 2 (plateau) of the action potential (7) was estimated by drawing tangent lines best fitted by eye to the slopes of phases 2 and 3; the interval from the end of phase 1 to the intersection of the tangent lines was considered phase-2 duration.

Epinephrine (bitartrate) was added either directly to the bath chamber with the inflow of Tyrode’s solution shut off or to the reservoir bottle of Tyrode’s solution.
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TABLE 1

<table>
<thead>
<tr>
<th>Hemodynamic Characteristics of Normal and Sham-Operated Cats and of Cats with Right Ventricular Failure</th>
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<tbody>
<tr>
<td>Peak RV systolic pressure (mm Hg)</td>
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<tr>
<td>-----------------------------------</td>
</tr>
<tr>
<td>Normal (7)</td>
</tr>
<tr>
<td>Sham operated (7)</td>
</tr>
<tr>
<td>Right ventricular failure (21)</td>
</tr>
</tbody>
</table>

The data for cats with right ventricular failure are from cats killed at least 10 days after partial pulmonary artery obstruction. Sham-operated cats were studied 3, 6, 7, 10, 12, 90, and 102 days after surgery. The number of cats studied in each group is given in parentheses. Data are expressed as means ± se. RV = right ventricular. *P < 0.05.

the latter case, disodium ethylenediaminetetraacetate was also added (5 × 10⁻⁵ M final concentration) to retard oxidation of the catecholamine. The data reported for the effects of epinephrine on transmembrane potentials were obtained during maintained impalements of single cells.

All results are expressed as means ± se. Student's t-test was used to determine if differences between the electromechanical properties of normal and failed muscles were significant (8). In our previous study, we noted that muscles from sham-operated cats had electrical and mechanical properties identical to those obtained for muscles from normal unoperated cats (3). The electrical and the mechanical properties of muscles from the normal and sham-operated cats reported in the present paper do not differ significantly from those previously reported.

Results

The hemodynamic characteristics of normal and sham-operated cats and of cats with right ventricular failure are shown in Table 1. Cats with right ventricular failure had significant right ventricular systolic hypertension (44.1 ± 7.0 mm Hg). Right ventricular end-diastolic pressure also was significantly elevated in these cats (12.0 ± 0.9 mm Hg). However, heart rate was similar for all three groups.

The wet weight of the right ventricular free wall of the hearts of cats with right ventricular failure increased about 40% (Table 2). Also right ventricular free walls obtained from cats with right ventricular failure showed an increase in myocardial water (Table 2); however, this increase did not account for the increase in wet weight, i.e., there was a real increase in myocardial protein during the development of right ventricular failure. There were no significant changes in the wet weight of the left ventricle and the septum of cats with right ventricular failure (Table 2).

For almost all muscles in cats with right ventricular failure, the peak force developed during contraction was decreased compared with peak force in normal cats. Furthermore, there were obvious alterations in the electrical properties of muscles from cats with right ventricular failure. After analysis of the experimental results, the data were grouped into several convenient, albeit somewhat arbitrary, categories. Group 1 included the majority of muscles from cats with right ventricular failure (13 of 21 muscles); all group 1 cats were killed ten days or more after pulmonary artery obstruction. The mechanical and electrical properties of the muscles from normal and sham-operated cats and of the muscles from group 1 cats are summarized in Table 3. Group 1 muscles showed a significant reduction (approximately 50%) in both the isometric active force at optimal length (P₀) and the maximum rate of development of force at optimal length, but time to peak force and duration of contraction were not significantly

TABLE 2

Ventricular Weights of Normal Cats and Cats with Right Ventricular Failure

<table>
<thead>
<tr>
<th>RV wt/body wt (g/kg)</th>
<th>RV wt (dry/wet) (g/kg)</th>
<th>LV + septum wt/body wt (g/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>0.62 ± 0.05 (7)</td>
<td>0.22 ± 0.01 (6)</td>
</tr>
<tr>
<td>Sham operated</td>
<td>0.64 ± 0.03 (8)</td>
<td>0.22 ± 0.01 (6)</td>
</tr>
<tr>
<td>Right ventricular failure</td>
<td>0.59 ± 0.10* (15)</td>
<td>0.19 ± 0.01* (15)</td>
</tr>
</tbody>
</table>

Data are expressed as means ± se. The number of cats studied is given in parentheses. The sham-operated cats are the same cats as in Table 1. RV = right ventricular free wall; LV = left ventricle. *P < 0.05.

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altered. Resting force was increased for group 1 muscles, but the increase was not statistically significant (Table 3). Although the mean cross-sectional area of group 1 muscles was greater than that of muscles from normal and sham-operated cats, the difference was not statistically significant (Table 3).

We observed changes in single-cell electrical characteristics of group 1 muscles. Figure 1 shows the transmembrane resting potential and the action potential recorded in a right ventricular muscle from a cat killed 15 days after partial pulmonary artery obstruction. Resting potential and action potential overshoot and maximum rate of rise were reduced compared with these parameters in normal cats. An increase in both total action potential duration and duration of phase 2 (plateau) was also observed; the plateau phase did not have the usual rounded configuration which occurs in normal muscles or muscles removed from sham-operated cats (Fig. 1). A depression in electrical characteristics was noted in 10 of the 13 muscles in group 1. The average resting potential and the action potential overshoot of group 1 muscles were decreased (approximately 9% and 30%, respectively); the decreases were statistically significant. Action potential rate of rise was also substantially reduced (24%). Phase-2 duration and action potential duration measured at 100% repolarization were significantly increased. Action potential duration at 70% repolarization was also increased, but the increase was not statistically significant. For three depressed muscles in group 1, we initiated field stimulation after determining the steady-state mechanical and electrical responses to point stimulation. During field stimulation, peak force developed during contraction increased slightly (6-13%) over peak force recorded with point electrodes; however, developed force was still below normal values.

The electrical depression did not depend on the time of study, i.e., a reduction in the magnitude of resting and action potential amplitude and action potential rate of rise was noted in group 1 muscles studied 10-15 days or 90-127 days after outflow tract obstruction. The remainder of the group 1 muscles (3 of 13) from cats with right ventricular failure showed normal resting potential and action potential overshoot and rate of rise and reasonably normal force characteristics.

For muscles listed in Table 3, we were unable to directly correlate the magnitude of right ventricular pressure measured in situ with the depression in electrical and mechanical characteristics in vitro. For example, we could not correlate the increases in ventricular end-diastolic pressures with the alterations in electrical properties. However, some changes were observed in the standard limb lead electrocardiograms of cats from which the group 1

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**TABLE 3**

<table>
<thead>
<tr>
<th>Cross-sectional area (mm²)</th>
<th>P₀ (g/mm²)</th>
<th>dP/dt (g/mm² sec⁻¹)</th>
<th>Time to peak force (msec)</th>
<th>Duration of contraction (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (8)</td>
<td>0.77 ± 0.06</td>
<td>1.12 ± 0.12</td>
<td>10.1 ± 0.3</td>
<td>146 ± 2.0</td>
</tr>
<tr>
<td>Sham operated (7)</td>
<td>0.72 ± 0.10</td>
<td>1.08 ± 0.09</td>
<td>9.2 ± 0.7</td>
<td>143 ± 4.0</td>
</tr>
<tr>
<td>Right ventricular failure (13)</td>
<td>0.90 ± 0.09</td>
<td>0.57 ± 0.05*</td>
<td>4.1 ± 0.3*</td>
<td>149 ± 4.0</td>
</tr>
</tbody>
</table>

Data are expressed as means ± se. The number of cats studied is given in parentheses. The sham-operated cats are the same as in Table 1. Resting force was measured at optimal length. P₀ = active force at optimal length.

*P < 0.05.

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<table>
<thead>
<tr>
<th>Resting force (g/mm²)</th>
<th>Resting potential (mv)</th>
<th>Overshoot (mv)</th>
<th>dV/dt, phase 0 (v/sec)</th>
<th>Phase-2 duration (msec)</th>
<th>Action potential duration</th>
<th>70% repolarization (msec)</th>
<th>100% repolarization (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.68 ± 0.18</td>
<td>84 ± 1.2</td>
<td>22.1 ± 2.4</td>
<td>164 ± 8</td>
<td>125 ± 2</td>
<td>186 ± 6</td>
<td>253 ± 7</td>
<td></td>
</tr>
<tr>
<td>0.69 ± 0.11</td>
<td>83 ± 0.9</td>
<td>21.2 ± 1.8</td>
<td>161 ± 5</td>
<td>122 ± 7</td>
<td>180 ± 4</td>
<td>264 ± 8</td>
<td></td>
</tr>
<tr>
<td>0.81 ± 0.14</td>
<td>77 ± 1.8*</td>
<td>15.0 ± 1.4*</td>
<td>125 ± 10*</td>
<td>152 ± 8*</td>
<td>207 = 12</td>
<td>302 ± 11*</td>
<td></td>
</tr>
</tbody>
</table>

Muscles were obtained. There was a pronounced shift of the frontal plane axis toward the right in the cats with long-term partial pulmonary artery obstruction; also, decreases in the magnitude of the QRS complexes, depressed S-T segments, and T wave inversion were observed. The right axis shift was not so evident in the cats with short-term pulmonary artery obstruction, but these cats often demonstrated minor electrocardiographic abnormalities, i.e., decreased QRS amplitude, changes in the S-T segment, and changes in the T wave. Electrocardiographic abnormalities were not evident in the three cats from which the muscles with reasonably normal force and electrical properties were obtained.

In some experiments, we recorded transmembrane potentials soon after initiating stimulation. The electrical characteristics of group 1 muscles often improved during the first hour of superfusion with Tyrode's solution (Fig. 2). However, after 1–3 hours of maintained superfusion, the electrical characteristics were 90–95% of the values obtained with long-term superfusion (3–4 hours).

Four muscles from cats with right ventricular failure generated very little, if any, active force, and these muscles had extremely depressed electrical characteristics: resting potential was substantially reduced, and often the electrical response to stimulation resembled local potential changes (Fig. 3). The mechanical and electrical properties of these group 2 muscles were as follows: cross sectional area 0.84 ± 0.04 mm², P 0.056 = 0.021 g/mm², resting force 0.96 ± 0.21 g/mm², resting potential 35 ± 6.2 mv, and action potential amplitude 29 ± 5.5 mv (compare with control and experimental data in Table 3). In two of these muscles, we reduced resting force markedly after 1½ hours and superfused them with Tyrode's solution for the next 2 hours. Little change in the electrical potentials was observed during this procedure. Again, as in the case of group 1 muscles, we were unable to relate the increases in right ventricular end-diastolic pressure to the electromechanical alterations shown in vitro by group 2 muscles. All four group 2 cats demonstrated marked electrocardiographic abnormalities similar to those outlined for group 1 cats. Group 2 muscles were obtained within a relatively short time after the banding procedure, i.e., 3–12 days after partial pulmonary artery obstruction.

Group 3 muscles (two) from cats with right ventricular failure displayed a reduction in the magnitude of their resting and action potentials; also, the action potentials had unusual configurations which resembled those recorded in mammalian ventricle during superfusion with a high-potassium solution (9, 10). There was a slow upstroke velocity, and phases 2 and 3 of the action potential were prolonged (Fig. 4).

Two additional muscles from cats with right ventricular failure formed group 4. These muscles...
Membrane potential (top trace) and isometric contraction (bottom trace) recorded in a group 2 failed ventricular muscle. **Left:** Control recordings. Note the marked depression of membrane potential and isometric force. **Middle:** Addition of epinephrine (EPI) to the superfusate induced an increase in membrane potential, possibly an active membrane response, and a slight increase in developed force. **Right:** During further exposure to the drug, an additional increase in membrane potential occurred, an action potential was elicited, and isometric force was markedly improved. Single impalement maintained throughout exposure to drug. RVF = right ventricular failure.

Transmembrane action potentials recorded in such muscles showed a prepotential on which a faster depolarization was superimposed (Fig. 5).

Previous studies indicate that epinephrine returns resting potential toward normal values in canine cardiac Purkinje tissue and human atrial muscle when resting membrane potential has been reduced by stretch (11–13), hypoxia (11–13), or treatment with excessive quantities of procaine amide (11–12). For three muscles in group 1 listed in Table 3, epinephrine ($10^{-6}$M) increased resting potential slightly (2–6 mV); maximum rate of rise of the action potential increased an average of 18.8 v/sec and peak active force increased an average of 176%. The increases in resting potential were much greater in group 2 muscles (Fig. 3). For two group 2 muscles, resting potential increased an average of 32.4 mV during exposure to epinephrine ($10^{-6}$M), and developed force increased an average of 258%; after sustained washing with control Tyrode's solution, resting potential approached the original depressed levels. Exposure to epinephrine ($5 \times 10^{-7}$M) increased resting potential and induced a rapid upstroke in the very slowly rising action potentials of group 3 muscles, and an alteration in the configuration of the action potential resulted (Fig. 4).

Exposure to epinephrine ($5 \times 10^{-7}$ to $10^{-6}$M) in normal cat right ventricular muscles produced marked increases in peak force developed during contraction with little, if any, hyperpolarization.

For three normal muscles, resting potential was $83 \pm 1.7$ mV before the addition of epinephrine ($10^{-6}$M) and $84 \pm 2.2$ mV during its maximum effect; peak active force, however, increased an average of 192%.
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**FIGURE 5**

Action potential (top trace) and isometric contraction (bottom trace) recorded in a group 4 muscle. Note the biphasic contraction. The action potential also demonstrated two phases. Note the slow depolarization and the faster depolarization superimposed on it. All cells studied in this muscle showed a biphasic action potential response.

**Discussion**

Clinically, congestive heart failure is a complex syndrome which results from single or multiple pathological factors in man. Myocardial failure, which develops over a period of time following sudden, experimentally induced, ventricular outflow tract obstruction in small mammals, in many ways resembles congestive heart failure in man (1, 2, 14, 15). The clinical condition and the experimental model display some similar mechanisms during the development of heart failure. For example, both the human and the cat heart demonstrate an increased muscle mass when a ventricle is continually stressed by an increased resistance to ventricular ejection (1). Despite these similarities, this model of right ventricular failure has limitations. Our model differs from the clinical situation with respect to heart rate. A reflex-mediated increase in heart rate is frequently observed in man during the development of congestive heart failure; the increase in heart rate is a compensatory mechanism which helps maintain cardiac output during this pathological state. However, we noted and Spann et al. (1) reported no significant increase in heart rate in cats with experimental pressure overload–induced right ventricular failure. More recently, Spann et al. (2) reported a decrease in heart rate during experimentally induced right ventricular failure in cats. This difference in heart rates between humans and cats in ventricular failure might be related to the effects of the anesthetic agents employed in the animal studies.

In the present study, ventricular muscles from three cats in apparently overt right ventricular failure had reasonably normal electromechanical properties. This finding also might be related to the adequacy of the experimental model. Our first definition of right ventricular failure was initially made on the basis of clinical physical examination. We then used a markedly elevated right ventricular diastolic pressure as the major determinant of right ventricular failure. The criteria we used to define this syndrome of right ventricular failure were scanty and rather arbitrary; possibly these three cats showed clinical and hemodynamic signs of right ventricular failure although their ventricular muscles were not particularly depressed. Furthermore, not all the cats were expected to be at the same level of ventricular failure and contractile impairment because of variations in the degree of banding and the intrinsic contractile state of the ventricle before banding. These two factors also explain, in part, the great variation in the time when any particular cat showed signs of right ventricular failure (1).

Various changes in electrical properties of right ventricular muscles removed from cats in experimental right ventricular failure were documented. There is no question that a number of cats with right ventricular failure also had significant degrees of ventricular hypertrophy as shown by the increase in the ratio of right ventricle weight to body weight. The depressed and altered potentials of the failed muscles were due to or, at least, related to the failure per se, since we never saw these particular resting potential and action potential changes in muscles from cats with right ventricular hypertrophy uncomplicated by failure. In the cats with ventricular hypertrophy without signs of right ventricular failure, a characteristic shift in the voltage level of the plateau phase which was most prominent three days after imposing the pressure overload was observed (3); all other measured transmembrane characteristics (resting potential and action potential amplitude, rate of rise, and duration) were normal. The characteristic shift in the plateau was much less obvious 10 days after sudden pressure overload and was never seen in muscles studied 14 days after partial pulmonary artery constriction (unpublished observations). Our previous results agree with those of Uhley (16), Konishi (17), and Kaufmann et al. (18), which also indicate that resting and action potential magnitude
and action potential rate of rise were unaltered in hypertrophied ventricular myocardium of several mammalian species. These data on single-cell electrical properties of isolated hypertrophied ventricle without failure are in accord with results from studies on intact dogs that reveal no changes in ventricular conduction velocity in situ during hypertrophy (activation time does increase in the hypertrophied canine right ventricle, but it is proportional to the increase in myocardial mass [19]).

The bases for the altered and depressed electrical characteristics during right ventricular failure are unclear at present. Acute excessive stretch decreases isometric force, resting potential, and action potential overshoot in cat papillary muscles studied in vitro; at extreme muscle lengths, the transmembrane electrical activity is similar to local potential overshoot in cat papillary muscles studied in vitro; at extreme muscle lengths, the transmembrane electrical activity is similar to local potential changes but dissimilar to propagated action potentials (20). These acutely altered electrical parameters return to or approximate the initial control values after the papillary muscle is released from excessive stretch (20). Group 2 muscles often showed potentials of the local response type. However, in contrast to acutely overstretched muscles, group 2 potentials showed little improvement after muscle length was substantially reduced.

There are significant changes in tissue fluids and electrolytes during congestive heart failure in man (4, 21, 22) and experimentally induced ventricular failure in dogs (23). Other studies indicate that sudden increases in afterload (increased aortic pressure) are accompanied by a net loss of ventricular potassium in isolated supported hearts (24). Although we have no direct evidence from our own experiments, possibly the intracellular sodium concentration was increased and the intracellular potassium concentration decreased in the muscles from cats with right ventricular failure. Such changes in ionic distribution might have been sufficient to reduce the resting potential and the action potential amplitude and rate of rise. The decrease in resting potential would also diminish the action potential rate of rise (25). These postulated changes in myocardial ionic concentrations might result from specific effects of the increased pressure load on the ventricle, or they might reflect generalized changes in muscle ionic composition similar to those recently reported for human skeletal muscle during severe disease (26).

Although we are uncertain of the direct cause of the depression in electrical properties, our data suggest that the depressed electrical activity might modify the contractile event. For the group 2 muscles from cats with right ventricular failure, the failure of some cells to be excited by the propagating action potential and the excitation of other cells by slowly rising small action potentials might have contributed to the decrease in active force developed by the muscles. The unexcited cells did not make their usual contribution to active force development, and the cells demonstrating low resting potential, resulting in the inactivation of the sodium-carrying system and the slowly rising action potentials, most likely had depressed conduction and caused a slower and less synchronous activation of the membranes of individual cells. Furthermore, the change in the voltage level and the duration of the plateau might be associated with a diminished calcium influx during excitation (27-29), and this low influx in turn might reduce the amount of calcium available for initiating contraction. For group 2 muscles, the electrical depression probably exacerbated the primary contractile defect noted in pressure overload-induced right ventricular failure. The electrical depression in group 1 muscles also exacerbated the intrinsic contractile defect but to a lesser extent. Stimulation of mass electrodes increased contractile force slightly in group 1 muscles, presumably because of a more synchronous activation of the population of cell membranes.

Catecholamines increase the force of contraction in normal mammalian myocardial muscle without significantly changing the magnitude of the resting potential (30-33 and this paper). The effect of epinephrine on group 2 muscles suggests that part of the positive inotropic effect of the catecholamine in failed myocardium with substantial electrical depression might result from a return of resting membrane potential toward normal levels. The basis of the striking effect of epinephrine on severely depressed resting potential is undetermined; possibly it is related to the stimulating effect of the catecholamine on the myocardial sodium-potassium pump (34) or to changes in membrane potassium conductance (35). In any event, partial restoration of resting potential by epinephrine results in an increased availability of sodium carrier; quiescent cells might become excitable and there might be a net recruitment of cells participating in the contractile event. Thus, contractility of experimentally failed ventricle would be improved by a combination of the usual inotropic actions of epinephrine and its marked restorative effects on
modified the contraction of the isolated myocardium. This explanation does not consider the possibility that epinephrine intervention also increases the slow inward current(s) in the failed muscles (35-37).

These data indicate that cellular electrical properties are depressed during right ventricular failure and that the altered electrical properties possibly modify the contraction of the isolated myocardium. The basis for the alterations in transmembrane potentials and their significance in relation to contractility of the intact heart remain to be determined.

References
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