Electrical Uncoupling and Increase of Extracellular Resistance After Induction of Ischemia in Isolated, Arterially Perfused Rabbit Papillary Muscle

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Extracellular and intracellular longitudinal resistances \( (\mathbf{r}_e \text{ and } r_i) \), transmembrane potentials, and conduction velocity were determined in arterially blood-perfused rabbit papillary muscles. Cable analysis was made possible by placing the muscle in a H\(_2\)O-saturated gaseous environment, which acted as an electrical insulator. Ischemia was produced by exchanging the \( \text{O}_2 \) in the atmosphere by \( \text{N}_2 \) (94\% \( \text{N}_2 \)-6\% \( \text{CO}_2 \)) in addition to arresting coronary flow. The first 10-15 minutes of ischemia were characterized by an increase in \( r_e \), while \( r_i \) remained constant. The early part of the increase in \( r_e \) coincided with the drop in perfusion pressure and was probably due to the diminution of intravascular volume. Rapid electrical uncoupling, reflected by an increase in \( r_i \) (threefold within 5 minutes), occurred thereafter. The dissociation between the early increase in \( r_e \) and the delayed increase in \( r_i \) produced an initial increase in the ratio \( r_e : r_i \), which subsequently decreased. The decrease in conduction velocity was less than observed in intact hearts with ischemia. This difference is explained by the relatively small changes in resting membrane potential and action potential amplitude in the preparation used. Our results suggest that in the early, reversible phase of ischemia, the increase in \( r_e \) contributes to a small but significant extent to the slowing of conduction. After 15-20 minutes, the rapid cellular uncoupling, which was most likely coincident with breakdown of cellular homeostasis, may contribute to the occurrence of arrhythmias during this phase of ischemia. Moreover, the early change in the ratio \( r_e : r_i \) will influence the amplitude of the extracellular electrograms following coronary occlusion (TQ-segment and ST-segment shifts). (Circulation Research 1987;61:271-279)

The existence of low resistance or diffusion pathways between cardiac cells\(^1,2\) is essential for normal cardiac function since it ensures the rapid propagation of the impulse (e.g., see Crane-field\(^3\)). Disruption of cells in myocardial necrosis was already noted in the last century by Engelmann.\(^4\) The association of electrical uncoupling in heart with mechanical injury was shown by Délèze,\(^5\) with intracellular calcium overload was shown by De Mello,\(^6\) with acidification was shown by Reber and Weingart,\(^7\) and with application of a cardiac steroid was shown by Weingart.\(^8\)

In ischemia, precise knowledge of the time course and the magnitude of electrical uncoupling is important to explain the decrease of conduction velocity and the formation of conduction blocks. Both are major causes of the malignant ventricular arrhythmias (e.g., see Janse and Kléber\(^9\)) that follow the interruption of coronary flow. Several indirect observations indicate that uncoupling develops relatively early in the course of myocardial ischemia: 1) Currents of injury, flowing across the boundaries between normal and ischemic tissue, decrease relatively rapidly after the first 15-30 minutes of ischemia.\(^10\) This suggests an increase of intercellular and/or extracellular resistive elements in the pathway of the injury current during the development of irreversible cellular damage. 2) In myocardial hypoxia, Wojtczak\(^11\) found a moderate (77\%) increase of intracellular longitudinal resistance (assuming a constant extracellular resistance) after 30 minutes of oxygen withdrawal. 3) The first morphologic sign of uncoupling, consisting of a separation of adjacent cell membranes at gap junctions, were reported to occur as early as 20 minutes after perfusional arrest.\(^12\)

Myocardial ischemia is characterized by, in addition to oxygen withdrawal, a lack of extracellular washout with a rapid extracellular accumulation of metabolic products and ions, e.g., potassium,\(^13\) and an increase in extracellular osmolality.\(^14\) An experiment arrangement to assess the changes in both extracellular and intracellular passive electrical properties of ischemic ventricle must be designed to fulfill two conditions. First, the myocardial tissue must be arterially perfused in its normoxic state, and second, the geometric arrangement of the cells must permit the application of linear cable theory.\(^15\) We have shown recently that these methodologic requirements are met in a blood-perfused rabbit papillary muscle surrounded by a gas mixture, which acts as an electrical insulator.\(^16\) In this preparation, a modification of the classic linear cable analysis for
Arterially Perfused Rabbit Papillary Muscle

Materials and Methods

Arterially Perfused Rabbit Papillary Muscle

Rabbits weighing 2–3 kg were anesthetized with 50 mg/kg pentobarbital i.v. and killed by a blow on the head. Heparin (200 U/kg) was administered intravenously, and the heart was rapidly excised and brought to a dissecting chamber. The basis of the heart (including both atria and the atroventricular valves) and the left ventricular free wall were removed with a razor blade. Afterwards, the septal artery was cannulated (e.g., Weiss and Shine1), and the nonperfused parts of the interventricular septum and the right ventricular free wall were carefully removed. The average time between excision of the heart and artificial perfusion was 4 minutes. The final preparation consisted of an arterially perfused part of the rabbit interventricular septum to which 2–3 papillary muscles usually were attached. Muscles selected for measurement had a single insertion of the tendon, a mean cross-sectional area of 1.12 mm² (±0.21 mm², SEM, n = 8) and showed no marked tapering at the apical end.

Perfusion and Recording Chamber

The perfusate contained a mixture of washed bovine erythrocytes (hematocrit 25%), albumin (2 g/l), dextran (70,000 MW, 40 g/l), insulin (1 U/l), heparin (400 U/l), and Tyrode’s solution of the following composition (in mM): Na⁺ 149, K⁺ 4.5, Mg²⁺ 0.49, Ca²⁺ 1.8, Cl⁻ 133, HCO₃⁻ 25, H₂PO₄⁻ 0.4, and glucose 20. The pH of the perfusion fluid ranged from 7.35–7.40. A detailed description and illustration of the perfusion apparatus and the recording chamber is given elsewhere.9 The perfusate was oxygenated in a membrane oxygenator and driven to the recording chamber by an Ismatec roller pump (Switzerland). The perfusion pressure within 10–15 seconds. To avoid diffusion of oxygen from the artificial atmosphere into

Production of Ischemia

Ischemia was produced by interruption of the arterial perfusion with a tap, which resulted in a total drop of perfusion pressure within 10–15 seconds. To avoid diffusion of oxygen from the artificial atmosphere into

and the base of the muscle. In 3 experiments, the developed tension was measured by a Hottinger Baldwin transducer (Darmstadt, Germany) fixed to the platinum wire. In such a way, an arterially perfused papillary muscle was obtained that was surrounded by the artificial atmosphere of the recording chamber, which acted as an electrical insulator. The artificial atmosphere consisted of an H₂O-saturated mixture of either O₂ and CO₂ or N₂ and CO₂ (see below), which flowed into the chamber through multiple holes drilled into the anterior and lateral walls. Temperature was maintained at 35°C by warming the tubing with the perfusion solution and the gas mixture in a water bath. Furthermore, the water of the thermostat was pumped through the partition of the double-walled cover of the recording chamber. An opening (1-cm diameter) in this cover allowed access to the preparation with the recording electrodes. Normally, a preparation remained mechanically and electrically stable for 6 hours when perfused under normoxic conditions. Within this period, no visible shrinking or swelling occurred as verified by microscopic control of the muscle diameter.

Circulation Research

Vol 61, No 2, August 1987
achieve complete mixing in the recording chamber. During ischemia, the residual partial O$_2$ pressure was less than 15 mm Hg in the first 4 experiments and less than 5 mm Hg in the rest of the experiments. This difference had no detectable effect on the electrical measurements. Only one ischemic period was produced per heart.

Measurement of Intracellular and Extracellular Longitudinal Resistances and Conduction Velocity

Both detailed description and a critical evaluation of the method used to determine passive cable properties have been published elsewhere. In essence, passive cable properties and conduction velocity were assessed with two sequential measurements. First, the extracellular voltage drop between two extracellular electrodes (E$_$ and E$_$) was recorded during application of a subthreshold constant current pulse (20 msec duration) that was applied extracellularly between the apical electrode and the electrode at the base (electrical ground, see Figure 1). The electrode E$_1$ was placed at a distance of 1.2 mm or greater from the insertion of the tendon. At this site, the subthreshold current that is injected into the extracellular space at the apical end is distributed regularly between the extracellular and intracellular compartments, and membrane current has become negligible. Therefore, the longitudinal tissue resistance $r$, which is composed of $r$ (intracellular longitudinal resistance) and $r$ (extracellular longitudinal resistance) in parallel, can be obtained from $V_o$, $\Delta x$, and $I$:

$$\frac{V_o}{\Delta x \cdot I} = r = \frac{r \cdot r_n}{r + r_n} \quad (\Omega/cm) \quad (1)$$

where $V_o$ is the subthreshold voltage drop between E$_1$ and E$_n$, $\Delta x$ is the interelectrode distance, and $I$ is the strength of the subthreshold current (see Figure 5 of Kléber and Riegger$^{16}$).

For the second set of measurements, an excitatory current pulse (0.5–1.0 msec in duration, double threshold strength, 30 msec after the subthreshold pulse) was applied to activate the apical end of the muscle. The cycle length between stimuli ranged between 500–800 msec among different experiments and remained constant during an experiment. During excitation, the extracellular bipolar electrogram was measured between the electrodes E$_1$ and E$_n$, and the transmembrane potential was measured between an intracellular floating microelectrode E$_1$ and the extracellular electrode E$_2$ (Figure 1). Conduction velocity $\theta$ was obtained from the interval between the deflection and the inflection of the bipolar electrogram and the interelectrode distance (for linearity of propagation, see Kléber and Riegger$^{16}$). The ratio of extracellular to intracellular longitudinal resistance $q$ was obtained from the absolute values of the amplitudes of the extracellular bipolar electrogram ($\Delta V_o$) and the transmembrane action potential ($\Delta V_m$):

$$q = \frac{|\Delta V_o|}{|\Delta V_m| - |\Delta V_o|} = \frac{r_o}{r} \quad (2)$$

where the values for $r_o$ and $r$ (in $\Omega$ cm) were calculated from equations 1 and 2. The values for the intracellular longitudinal specific resistance $R_o$ ($\Omega$ cm), extracellular longitudinal specific resistance $R$ ($\Omega$ cm), and specific tissue resistance $R$ ($\Omega$ cm) were calculated during normoxia from the measured cross-sectional area of the muscle and from an assumed extracellular: intracellular space ratio of 1:3. During ischemia, the measurement of the specific resistances was not possible because of the lack of morphometric information on volume changes in the extracellular and intracellular compartment. Therefore, the results were expressed in percent of the $r$, $r_o$ values during normoxic perfusion. The paired $t$ test was used for comparison of results after a given duration of ischemia and of results during normoxic perfusion. Summarized results are expressed as mean ± SEM.

Extracellular electrodes (50 μm tungsten wire) and intracellular electrodes (floating glass microelectrodes, see Kléber and Riegger$^{16}$) were connected to high input impedance buffer amplifiers (Analog Device 515), and signals were amplified by differential instrumentation amplifiers. Current strength was measured in the feedback loop of an operational amplifier introduced between the preparation and ground. The amplified traces (current strength and extracellular and intracellular voltage) were stored digitally in a signal memory recorder (Max Meyer Electronics, Switzerland) at a sampling rate of 100 μsec (subthreshold events) or 30 μsec (suprathreshold events). The data were analyzed by a Hewlett-Packard Model 9617 computer and were displayed on a graphic plotter. The interelectrode distances were measured with a micrometer in the eyepiece of the binocular microscope (magnification, 25×).

Results

Extracellular and Intracellular Resistivities and Potentials During Normoxic Perfusion

Figure 2 shows recordings during flow of subthreshold current (left panel) and after excitation of the apical end of the muscle (right panel) when the muscle was arterially perfused. The distance $\Delta x$ between the extracellular electrodes was 2.24 mm in this experiment. The apical extracellular electrode was placed 1.32 mm from the end of the muscle, which is about three times the estimated space constant (Kléber and Riegger$^{16}$). With this position of the electrodes (remote from the zone of transmembrane current flow during application of the subthreshold current), the longitudinal tissue resistance $r$, is obtained directly from the subthreshold voltage displacement, the current strength, and $\Delta x$. The ratio $r/r$ (1.38) was calculated from the amplitudes of intracellular and extracellular potentials (98 and 57 mV, respectively). In this case, the resistance values, expressed in terms of specific
Longitudinal resistances, were $R_i = 97 \ \Omega \ \text{cm}$, $R_o = 70 \ \Omega \ \text{cm}$, and $R_t = 115 \ \Omega \ \text{cm}$. Expressed this way, the longitudinal resistor has the same order of magnitude as the intracellular longitudinal resistor, as is evident from the ratio $r_o : r_i$.

**Changes of Extracellular and Intracellular Longitudinal Resistances During Ischemia**

The change in the resistances of the tissue compartments are expressed in relative changes in $r_o$ and $r_i$. This was necessary because calculation of the specific resistances ($R_o$ and $R_i$) requires an assumption of the actual ratio of extracellular:intracellular space. This ratio changes during ischemia\(^{14}\) but has not been assessed in our preparation.

Figure 3 shows the mean values from 8 experiments of changes in the extracellular longitudinal resistance. In this and subsequent figures, mean values were taken from measurements within successive 2-minute time intervals. Following arrest of coronary flow, there is an immediate increase in extracellular resistance of approximately 30%. In later stages of ischemia, a second gradual increase occurs to levels of +60% after 20 minutes. The immediate increase in $r_o$ coincides with the drop in perfusion pressure and the resulting fall in intravascular volume. Figure 4 shows that the loss of the hydraulic stiffness ("garden hose effect")\(^{20}\) also gives rise to a considerable fall in actively developed tension. This fall in tension associated with the arrest of perfusion, as measured in three experiments, was 31 ± 4%.

The changes in intracellular longitudinal resistance are shown in Figure 5. In Figure 5A, the changes are plotted vs. time elapsed after the arrest of coronary perfusion. In the first 10–12 minutes, intracellular resistance remains constant; in later stages, there is a steep increase. In individual experiments, this increase occurred very rapidly at times varying between 12–18 minutes after interruption of coronary flow. To eliminate this variability and to visualize the average time course of the onset of uncoupling, the same data were replotted in Figure 5B by superimposing the individual values between +20 and +30% into one window on a relative time scale. This shows that there is a mean increase in intracellular longitudinal resistance of +200% within 5 minutes.

The calculation of $r_o$ and $r_i$ requires linear cable properties, which implies uniform continuous propagation of the impulse. At a certain time and a certain

![Figure 2](image-url)

**Figure 2.** Left panel: Subthreshold current pulse (upper trace) of 20-msec duration flowing longitudinally through muscle and producing subthreshold voltage drop (lower trace) between extracellular recording electrodes $E_1$ and $E_2$. Longitudinal tissue resistance $r_i$ (consisting of $r_m$ and $r_e$ in parallel) is calculated from current strength, subthreshold voltage, and interelectrode distance. Right panel: Bipolar extracellular electrogram (upper trace) and initial portion of transmembrane action potential (lower trace). Ratio of extracellular to intracellular longitudinal resistance $r_o : r_i$ is calculated from amplitudes of extracellular and intracellular signals. Values for $r_o$ and $r_i$ are obtained from $r_m$ and ratio $r_o : r_i$. Conduction velocity is calculated from conduction time (time between deflection and inflection of extracellular electrogram) and interelectrode distance.

![Figure 3](image-url)

**Figure 3.** Changes of extracellular longitudinal resistance after arrest of coronary flow. Mean values (bars indicate standard error) from 8 experiments (8 hearts). First stepwise increase within first minute is followed by slower continuous increase. Changes are significantly different from control ($p<0.01$) at all time intervals.

<table>
<thead>
<tr>
<th>$\Delta V_m$ (mV)</th>
<th>$\Delta V_e$ (mV)</th>
<th>$r_o : r_i$</th>
<th>$R_i$ ((\Omega \ \text{cm}))</th>
<th>$R_o$ ((\Omega \ \text{cm}))</th>
<th>$R_t$ ((\Omega \ \text{cm}))</th>
<th>$\Theta$ (cm/sec)</th>
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<tbody>
<tr>
<td>$n$</td>
<td>8</td>
<td>8</td>
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<tr>
<td>Mean ± SEM</td>
<td>102 ± 3</td>
<td>53 ± 4</td>
<td>1.1 ± 0.1</td>
<td>126 ± 11</td>
<td>194 ± 31</td>
<td>66 ± 6</td>
</tr>
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</table>

$\Delta V_m$ and $\Delta V_e$, amplitudes of transmembrane action potential and extracellular electrogram, respectively; $r_o : r_i$, ratio of extracellular:intracellular longitudinal resistance. Calculation of longitudinal specific resistances for whole tissue ($R_t$), intracellular space ($R_i$), and extracellular space ($R_o$) were based on assumed extracellular volume fraction of 0.25.\(^{18}\) $\Theta$, conduction velocity.
degree of uncoupling (as indicated by the dot in Figure 5A), propagation became discontinuous, which prevented calculation of \( r \) and \( r_0 \). This discontinuity was apparent from irregularities (notches) on the upstrokes of intracellular potentials and/or fragmented extracellular electrograms. Since measurements of the sub-threshold events were independent of propagation, a further and rapid uncoupling was indicated by the continuous increase of total longitudinal tissue resistance \( r \), beyond this point (not shown).

The changes in extracellular and intracellular resistances have consequences for the propagation of the impulse and for the magnitude of extracellular potential changes during the flow of injury current across an ischemic boundary. Local current produced by a propagating wave front flows through a resistor that is composed of the intracellular and extracellular resistances in series. During ischemia, this series resistance increases immediately following arrest of coronary flow. As shown in Figure 6 (top trace), during the first 10 minutes of ischemia, this increase is entirely accounted for by the change in the extracellular resistance, while the change in intracellular resistance only contributes thereafter. In the lower part of Figure 6, the ratio \( r_0 : r \) is plotted. This ratio increases from 1.1 to 2.1 in the first 10 minutes, reflecting the increase in \( r_0 \). Subsequently, the increase in \( r \) causes the ratio to decrease. These changes must be taken into account for the interpretation of extracellular potential changes (TQ- and ST-segment shifts) during regional ischemia (see “Discussion”).

Each muscle was reperfused after 25 minutes of ischemia. This produced rapid visible swelling, interstitial accumulation of erythrocytes, and contracture. Assessment of cable properties was not possible because of the irregular shape of the extracellular electrograms, which may reflect either inhomogeneities in the extracellular resistor or persistence of cellular uncoupling. However, action potentials of normal...
FIGURE 6. Top panel: Changes of series resistor ($r_s + r_t$) after induction of ischemia. Lower area indicates contribution of $r_s$; upper area indicates contribution of $r_t$. Changes at all time intervals were significantly different from control ($p<0.05$). Bottom panel: Changes of ratio $r_s/r_t$ in ischemia. Changes after 1-14 minutes were significantly different from control ($p<0.01$ between 1-12 minutes, $p<0.05$ between 12-14 minutes).

Changes in Transmembrane Potentials

Figure 7 shows extracellular bipolar electrograms (upper panel) and transmembrane potentials (lower panel) from an experiment in which it was possible to maintain the intracellular impalement for 25 minutes and to place the extracellular reference electrode as close as 40 μm to the intracellular microelectrode.

The delayed activation of the impaled cell during ischemia is clearly visible. The increased conduction time is apparent from the increased interval between downstroke and upstroke of the bipolar electrogram. After 25 minutes of ischemia, action potential amplitude had decreased by 18 mV. At this time, the upstroke amplitudes could consistently be recorded after reperfusion.

Discussion

The methods used in the present study were designed for the assessment of electrical activity and of cable properties in densely packed, arterially perfused ventricular muscle. The preparation used offers two advantages: 1) It allows measurements of the effects of ischemia, and 2) it excludes the effects of an extracellular shunt resistance made up by a small layer of superfusion fluid in in vitro preparations or by cavity...
extracellular longitudinal resistance, which is slightly higher than the value for intracellular longitudinal resistance. This finding implies that changes in electronic interaction between ventricular cells are dependent to an equal degree on the resistances of intracellular and extracellular spaces.

Arrest of coronary flow resulted in an almost immediate increase in extracellular resistance. This increase appears not to be related to metabolic changes since it has also been observed in fibers exposed to an atmosphere containing 94% O2. It is most likely due to the fall in perfusion pressure and to the associated decrease in intravascular volume. The mechanical consequence of arrest of perfusion, which in our preparation was a reduction of twitch tension by 30%, has been termed loss of hydraulic stiffness or garden hose effect in hearts in vivo. For both measurements, changes were significantly different from control at all time intervals (p<0.05).

The second increase (indicating onset of irreversibility) occurs at a time similar to the increase in intracellular resistance. The change in the ratio r/c-r, may have important implications for the interpretation of the magnitude of extracellular potentials recorded across an ischemic boundary in hearts with regional ischemia. The instantaneous difference in transmembrane potentials between normal and ischemic cells provides the driving force for the injury current flowing through the intracellular and extracellular resistances across an ischemic border. This driving force is divided between the intracellular and extracellular resistances. The voltage drop over the extracellular resistance builds up the extracellular field. At a given driving force, the initial increase in the ratio r/c-r observed in our experiments will result in an increase in the extracellular component (TQ-segment depression and ST-segment elevation). While the subsequent decrease of this ratio will decrease the changes in the extracellular field, i.e., the amplitudes of the extracellular electrograms.

The reduction in action potential amplitude and observed at the intercalated disk. They consist in a migration of vesicular bodies toward the intercalated disk and in a dissociation of the gap junctional membranes. The reasons for cellular uncoupling, which was not reversible after 25 minutes, can be manifold. Both a decrease in intracellular pH and an increase in intracellular calcium are likely to play important roles. No information is available on eventual additional effects of metabolites produced during ischemia on nexal resistance. An association with an increase of free intracellular Ca2+, and probably Na2+, is most likely. Thus, the delayed increase in coupling resistance in our experiments corresponds in time to the delayed increase in resting tension in ischemic rabbit interventricular septa, which may be caused by an increase in free Ca2+. The relation with the breakdown of ionic homeostasis is further suggested from measurements of cellular K+ loss. Accumulation of extracellular potassium occurs in two distinct phases. The second increase (indicating onset of irreversibility) occurs at a time similar to the increase in intracellular resistance.

Our experiments show that ischemic myocardial cells uncouple rapidly after an initial stable phase of 10-15 minutes, during which intracellular longitudinal resistance remains unchanged. This finding adds further support to the views that the ionic homeostasis of acutely ischemic cells is not markedly disturbed and, particularly, that there is no marked increase of intracellular free Ca2+ during an initial phase of about 10-15 minutes after coronary artery occlusion. In line with this result are findings of maintained low intracellular Na+ activity in guinea pig hearts and of low resting tension in early ischemia in rabbit interventricular septa. Functional uncoupling after 10-15 minutes correlates well with the first morphologic changes...
resting membrane potential were considerably less than that observed in intact hearts with global or regional ischemia. An eventidal contamination of the gaseous atmosphere within the recording chamber by diffusion of oxygen can be ruled out; oxygen pressure was carefully monitored and found to be lower than 15 mm Hg in the first 4 experiments and less than 5 mm Hg in the remaining 4 experiments. A major difference between our preparation and thick-walled intact ventricles during ischemia is the partial pressure of CO2 in the tissue. It is known that pco2 rises rapidly and continuously to values between 200 and 400 mm Hg within 15 minutes following coronary artery occlusion. In our preparation, Pco2 was kept low by the constant CO2 content of the atmosphere (6%) around the muscle that was continuously exchanged. It has been shown that both extracellular K+ accumulation and depolarization of resting membrane potential can be modulated by varying Pco2 in the subepicardial layers of the globally ischemic guinea pig hearts. This interaction appears to occur between CO2 (or H+) and passive K+ efflux because active K+ influx remains unaffected during the early phase. The exact way a change of pco2 or pH interferes with cellular K+ loss in ischemia remains to be clarified, however.

The contribution of the changes in extracellular and intracellular resistances on the changes in conduction velocity was calculated according to linear cable theory. The predicted overall effect was a steady decrease in conduction velocity by 12% after 10 minutes and by 23% after 20 minutes. A comparison with the actually measured changes in conduction velocity in our preparation indicates that the changes in conduction are additionally related to other factors in a complex way. In the first 4 minutes, there was no significant change in conduction velocity, while a small decrease was predicted by the increase in rL. In later stages, measured conduction velocity was consistently lower than expected from the increase in rL alone. The present data do not allow the contribution of the changes in action potential and excitability to be assessed in a quantitative way. An initial decrease in current requirement for excitation due to the shift of the resting membrane potential towards the threshold potential has been considered as a factor preventing an early decrease in conduction velocity. In later stages of ischemia, changes in action potential upstroke characteristics as well as a decrease in excitability are likely to contribute to conduction slowing. In our experiments, action potential amplitude decreased by 10–20%. A correlation of conduction velocity with changes in maximal upstroke velocity could not be carried out in our experiments. A precise measurement of maximum upstroke velocity was possible in only a few experiments (Figure 7) because of interference with the large extracellular field. Distortion of the action potential upstroke was noted whenever the extracellular reference electrode was placed further than about 80 µm from the impalement site.

The changes in conduction observed in intact ventricles with acute ischemia are different from those in the present experiments. Within 4–5 minutes, longitudinal conduction velocity decreases to 50% of the control value, and conduction blocks occur within the same period. Conduction block is cycle-length dependent in the sense that zones which block the impulse at short cycle lengths can conduct the impulse upon a sudden increase in cycle length. This indicates that the delayed, time-dependent recovery of excitability is the most important determinant of conduction block. The marked decrease in action potential amplitude and upstroke velocity and the time-dependent recovery of excitability occur only in ischemic cells that are depolarized to a critical degree. The possible reasons for the absence of this marked shift of resting potential in our preparation have been discussed above.

In conclusion, the increase in extracellular resistance in the first 10 minutes of ischemia contributes to a small but significant extent to the decrease in conduction velocity during the acute reversible phase of ischemia. Reentrant excitation in the ventricular wall during this phase will be predominantly caused by the effect of ischemia on the electrical activity of the membrane (changes in action potential upstroke and in excitability). After 15–20 minutes, the rapid uncoupling of the ischemic cells is likely to contribute to the disturbances of impulse conduction, which may be important factors for the occurrence of arrhythmias during this and subsequent periods.

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doi: 10.1161/01.RES.61.2.271

_Circulation Research_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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