Changes in conduction velocity during acute ischemia in ventricular myocardium of the isolated porcine heart


ABSTRACT Conduction velocities along longitudinal ($v_l$) and transverse ($v_t$) fiber axes were determined in isolated porcine hearts from subepicardial activation patterns that were produced by local stimulation and measured with a multiterminal electrode. In some of the experiments extracellular $[K^+]$ ($[K^+]_o$) and transmembrane potentials were recorded. During normal perfusion $v_l$ and $v_t$ were (cm/sec) 50.08 ± 2.13, (SE) and 21.08 ± 0.97. After 3 to 5 min of global ischemia, $v_l$ and $v_t$ decreased to approximately 30 and 13 cm/sec. Before the occurrence of total inexcitability propagation became time dependent (1) 2:1 block developed and (2) centrifugal spread from the stimulus site was partially blocked at short intervals and was normal at long intervals. This suggested that slowed conduction was dependent on spatial nonuniformities of recovery from excitability. Slowing of conduction during ischemia was not explained by accumulation of $[K^+]_o$, alone, because $v_l$ and $v_t$ at a given $[K^+]_o$ were lower during ischemia than during perfusion with elevated $K^+$. In hearts perfused at 20 mM $[K^+]_o$ "slow responses" were produced by addition of epinephrine ($2.5 \times 10^{-5}$M). Resting membrane potentials of slow responses were significantly lower than of depressed action potentials during ischemia. The values $v_l$ and $v_t$ of slow responses (10 and 5 cm/sec) were much lower than the lowest values during ischemia (20 and 10 cm/sec). This indicates that slow conduction in ischemia is associated with depressed action potentials initiated by a partially inactivated rapid Na$^+$ inward current. The time dependence of nonuniform propagation and the relatively high conduction velocities explain two major characteristics of reentrant tachycardias in acute ischemia: (1) the large diameters of reentrant circuits and (2) the beat-to-beat changes in localization of conduction block.


THE HIGH INCIDENCE of ventricular tachycardia and ventricular fibrillation is one of the characteristic features of acute, reversible myocardial ischemia. During these arrhythmias propagation of the cardiac impulse occurs in multiple circus movements and reentrant excitation is responsible for maintenance of recurrent electrical activity. The electrophysiologic conditions necessary for these disturbances of cardiac rhythm were described at the beginning of this century. In early myocardial ischemia circulating excitation occurs around a zone of block that may be purely functional in nature. The dimensions of the circus movements in such a case are determined by the product of conduction velocity and refractory period. Slowing of conduction greatly enhances the probability of occurrence of arrhythmias.

Delayed activation of an ischemic zone indicating a decrease of conduction velocity and/or a change in activation pattern of the ischemic tissue has been noted by many investigators. However, conduction velocity was not measured directly. Furthermore, the relationships between the decrease of conduction velocity, the changes in electrical activity at a cellular level, and ionic shifts, such as accumulation of extracellular $K^+$ are not fully evident.

The present experiments were carried out to quantify the changes in conduction velocity of ventricular myocardium during the acute, reversible phase of myocardial ischemia. To account for the effect of tissue anisotropy on conduction, velocities were measured on the longitudinal ($v_l$) and transverse ($v_t$) axis of the cardiac fibers. In some of the experiments epicardial $K^+$ concentration was measured simultaneously with $v_l$ and $v_t$ during ischemia and during perfusion...
with elevated \([K^+]_o\). In this way the contribution of accumulation of \([K^+]_e\) to conduction slowing was assessed. Furthermore, conduction during ischemia was compared with that of impulses that were initiated by slow inward current. Propagation by so-called slow responses was elicited by reactivating inexcitable hearts perfused at 20 mM \([K^+]_e\) with epinephrine. Finally, in a number of experiments transmembrane potentials were recorded, primarily to determine the level of resting membrane potential at which ischemic cells became inexcitable and the level of resting membrane potential at which slow responses could be initiated.

Methods

Preparation. Pigs weighing about 20 kg were anesthetized by intravenous injection of sodium barbital (20 mg/kg). After a midsternal thoracotomy, heparin (1000 U) was administered intravenously and blood was collected. Simultaneously, 1 liter of a modified Tyrode’s solution was infused through a femoral vein. In such a way 1500 ml to 1700 ml of a blood-Tyrode’s mixture was obtained, which was then used to perfuse the isolated heart. After this sampling procedure the heart was removed from the animal and connected to an apparatus where it was perfused according to the Langendorff technique. The flow rate varied between 100 and 120 ml/min/100 g tissue. Details of the perfusion system and of the composition of the blood Tyrode’s mixture are given elsewhere.

Measurement of conduction velocities. Conduction velocities during ischemia were measured on the epicardial surface of the anterolateral wall of the left ventricle. At this site, a multiple-terminal electrode was brought into contact with the epicardial surface. The electrode was composed of 64 (four experiments) or 96 terminals (12 experiments), which were arranged in a square lattice (figure 1). The distance between the terminals was 2.5 mm (64 terminals) and 1 or 1.2 mm (96 terminals). A single terminal consisted of a hole (diameter 50 to 100 \(\mu\)m) drilled into a block of polyvinylchloride (PVC). The channel obtained in this way was in continuity with a PVC tube (inner diameter 400 \(\mu\)m) of 20 cm in length. The tube contained a fine silk thread and was filled with isotonic saline and connected to an Ag/AgCl bridge. Thus, the whole electrode assembly allowed the simultaneous measurement of multiple unipolar direct-current (DC) electrograms from the epicardial surface with reference to a common DC potential. This potential was measured by a wick electrode fixed to the aortic root.

Before each experiment the longitudinal axis of the electrode was adjusted to be approximately in parallel with the longitudinal axis of cardiac fiber orientation. This was done by analyzing the waveforms of the extracellular electrograms. After central stimulation the signals on the longitudinal axis exhibit the largest initial R waves, whereas the signals along the transverse axis have no initial positive deflection during ventricular depolarization. Furthermore, the relationship between fiber orientation and electrode position was verified in two experiments by taking histologic sections of the subepicardial tissue.

Elliptic spread from the center of the multiple terminal electrode was produced by cathodal stimuli (5 msec pulse width) at double diastolic threshold strength. An electrode placed at a remote site in the left or right ventricle served as the anode. The stimulation rate in each experiment was selected to be slightly above the spontaneous rate of the sinoatrial node. In addition, the right atrium was stimulated synchronously to avoid interference between atrial and ventricular rhythms. Cycle length ranged from 350 to 700 msec in the various experiments.

The simultaneously recorded DC electrograms were processed as follows: After preamplification, differential DC amplifiers measured the difference in potential between each terminal and the common reference potential at the aortic root. The outputs of those amplifiers were connected to a high-speed multiplexing A/D converter (sampling rate 1/msec for each individual signal, sampling time 1 sec) and written into a circular buffer. Analysis of the data was performed with a PDP-11/34 computer. Extracellular electrograms were displayed in groups of five on a Megatec graphic display and the moments of activation (intrinsic deflection) were indicated on the screen with a joy stick. The beginning of the stimulus artifact on the signals was taken as the zero time reference for calculation of the activation times. A computer printout providing a two-dimensional array

![FIGURE 1. Left. Epicardial activation after central stimulation as represented by an isochronal map. Dots indicate individual recording electrodes. Interelectrode distance was 1.2 mm. Position of the central stimulus electrode is indicated by a quadrangle. Activation is shown in increments of 2 msec for a normally perfused heart; the central isochrone represents activation sites after 8 msec. Right. Recordings of unipolar electrograms during ventricular depolarization that served as a basis for the construction of the isochronal map. Electrode 60 was located on the longitudinal axis and electrode 6 on the transverse axis of the fibers, as indicated on the left. Activation times were taken from the onset of the stimulus artifact to the steepest part of the intrinsic deflection.](image-url)
of the electrode terminals with the activation time given for each terminal served as basis for the construction of isochronal maps (figure 1). Conduction velocities along the two axes of the ellipse were calculated from the distance separating the isochronal and the difference in activation times indicated by the isochrones (from outside the central 2.0 to 2.5 mm on the longitudinal axis and outside the central 1.0 to 1.5 mm on the transverse axis).

For a single map, the mean of the two values obtained for each axis was taken as \( v_1 \) or \( v_2 \) during elliptic spread. For this analysis, it was assumed that the centrifugal spread that occurred in three dimensions was not significantly different from the spread of a homogeneous parallel wave front. This might be erroneous in the sense that an elliptic wavefront has to deliver excitatory local current not only in its main direction of propagation (e.g., in the direction of the longitudinal axis), but also to deeper tissue layers and to tissue situated aside of the wave front peak. We cannot exclude the possibility that spread into the depth of the ventricular wall influenced our results. Regarding an eventual discrepancy between parallel two-dimensional and elliptic two-dimensional spread, it has been shown that differences are negligible outside the distances from the central electrode indicated above.\(^{15}\)

Statistical comparison of mean values (\( v_{1.0} \), \( v_{2.0} \), and \( v_{1.5} \)) at different times or different \([K^+]_0\) was done by analysis of variance.

**Measurement of \([K^+]_0\) and transmembrane potentials.** In 10 of 16 hearts \([K^+]_0\) concentration was measured simultaneously with \( v_1 \) and \( v_2 \) by means of an ion-selective electrode. The potassium electrode consisted of two PVC tubes fixed to the epicardial wall with a thin stainless steel needle close to the multiple electrode. One tube served as reference and was filled with Agar containing isotonic NaCl solution. The other tube served as a \( K^-\)-sensitive barrel. It was sealed at the tip with a PVC-vinylonimycin membrane and filled with 100 mM KCl. Both barrels were connected to a high-input impedance preamplifier (Analag Device 515) via Ag/AgCl bridges. The difference in potential between the two barrels was sensitive to the activity of \([K^+]_0\) ions. In the Results and Discussion section the measured \( K^+ \) activity will be given in terms of \( K^+ \) concentration, to which it is related by an activity coefficient of 0.746.\(^{16}\) For details on fabrication and calibration see Hill and Gettes.\(^{17}\)

In four hearts, transmembrane action potentials from subepicardial tissue layers were measured (simultaneously with \([K^+]_0\) and activation maps) by means of conventional floating microelectrodes (for methodologic details see Downar et al.\(^{17}\)).

**Experimental protocol.** Global ischemia was induced by total interruption of flow to the aortic cannula. In a single heart two ischemic periods were produced, each lasting between 3 and 7 min. Reperfusion was started after occurrence of inexcitability or ventricular fibrillation. Defibrillation was carried out with a standard device (energy 10 to 20 W/sec). A minimal interval of 30 min was observed between consecutive ischemic periods. In 10 heart activation maps \([K^+]_0\) and occasionally transmembrane potentials were measured during perfusion at elevated \([K^+]_0\). Usually three to four steady-state \([K^+]_0\) levels between 4.5 and 14 mM were obtained after equilibration of concentrated (1M) KCl solution added stepwise to the "venous pool" of the perfusion fluid. Propagation of action potentials initiated by slow inward current was produced in six hearts by increasing the \([K^+]_0\) in the perfusate up to approximately 20 mM and adding epinephrine (2.5 \( \times \) 10\(^{-3}\)M).

**Results**

Conduction velocities (\( v_1 \) and \( v_2 \)) after arrest of coronary flow. The change in impulse propagation during acute ischemia was characterized by two distinct phases. In the first phase, lasting between 3 and 5 min, stimulation was followed by regular elliptic spread from the central stimulus electrode. In a second phase a transition from slowed elliptic spread to complete inexcitability of the tissue occurred, which was characterized by partial block of spread from the center and by the occurrence of complete excitation block in a 2:1 fashion and to a progressively higher degree.

Reliable recordings were obtained in 13 hearts during the first and in eight hearts during the second ischemic period. In the remainder of cases the measurements had to be discarded because of dislocation of the electrode. The time course of \( v_1 \), \( v_2 \), and \( v_{1.5} \) \( v_{2.0} \) (phase of regular elliptic spread) is illustrated in figure 2 and table 1 for the first and second ischemic periods. Values for \( v_1 \) and \( v_2 \) during normal perfusion were not significantly different before the first and the second occlusion, indicating that the effects of a brief ischemic period on \( v_1 \) and \( v_2 \) were completely reversible. The changes in \( v_1 \) and \( v_2 \) during the first two min of ischemia showed considerable variability in different experiments. An increase of \( v_1 \) and \( v_2 \) occurred seven of 13 times during the first and seven of eight times during the second ischemic period. In the other experiments the velocities remained stable or decreased moderately during the initial 2 min. As a consequence, the mean changes in \( v_1 \) and \( v_2 \) were not significant. Afterwards \( v_1 \) and \( v_2 \) decreased significantly. The values obtained before the occurrence of 2:1 block and incomplete central spread were similar in both ischemic periods: \( v_1 \) decreased to 31 to 33 cm/sec and \( v_2 \) decreased to 13 cm/sec (table 1). However, the transition occurred earlier in the first than in the second period. During the first period inexcitability began to develop between 3 and 4 min in three experiments, at between 4 and 5 min in two experiments, and after 5 min in one experiment. During the second phase inexcitability started to develop in four hearts at between 4 and 5 min and in two hearts after 5 min. In the other cases ventricular fibrillation occurred before the transition to inexcitability. During both periods \( v_1 \) and \( v_2 \) changed by the same relative amount, i.e., there were no significant changes of the ratio \( v_{1.5} : v_{2.0} \).

In the course of myocardial ischemia, action potential upstroke and amplitude become markedly time dependent. Therefore, time dependency of \( v_1 \) and \( v_2 \) was expected to develop. In the first phase (regular elliptic spread) the time course of the velocity changes was not dependent on cycle length. This was analyzed by comparing the velocity values of two subgroups during the first ischemic period, with one subgroup...
including the values at short cycle lengths (330 to 400 msec, \( n = 4 \)) and the other including the values at long cycle lengths (500 to 700 msec, \( n = 4 \)). The effect of an abrupt increase in cycle length on \( v_L \) and \( v_T \) during slowed but regular elliptic spread was tested in two experiments and was relatively small. On a sudden increase of cycle length from 400 to 700 msec, \( v_L \) (cm/sec) increased moderately from 28 to 31 and from 20 to 23 and \( v_T \) (cm/sec) increased from 10 to 17 and from 9 to 11.

A special attempt was made to analyze propagation at the transition of slowed but regular elliptic spread to the state of inexcitability, since this phase might be pertinent for the explanation of the mechanisms of arrhythmias. The duration of this phase ranged from 30 sec to 2 min. The transition was characterized by the two following events that both indicated development of time dependency: (1) The appearance of total inexcitability of the tissue in a 2:1 fashion and its progression to a higher degree. An increase of stimulus strength to up to 10-fold the original value occasionally reversed 2:1 responses to 1:1 responses for a few beats. However, there was no basic change in the conduction pattern observed under the electrode. (2) The occurrence of incomplete spread from the central electrode resulting in change of the propagation pattern under the electrode matrix. The regular elliptic spread shown in figure 3, A, was recorded 4 min after the onset of ischemia (\( v_L \) 30 cm/sec; \( v_T \) 15 cm/sec). Stimulation of the same site after 5 min resulted in a failure

### TABLE 1

Acute myocardial ischemia: \( v_L \), \( v_T \), and the ratio \( v_L \cdot v_T \)

<table>
<thead>
<tr>
<th>Time after onset of ischemia (min)</th>
<th>0 ( (n = 13; n = 8) )</th>
<th>1 ( (n = 11; n = 7) )</th>
<th>2 ( (n = 10; n = 8) )</th>
<th>3 ( (n = 12; n = 8) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( v_L ) ( \pm SE )</td>
<td>50.08 ( \pm 2.13 )</td>
<td>50.00 ( \pm 2.87 )</td>
<td>50.10 ( \pm 2.42 )</td>
<td>38.42 ( \pm 2.94 )</td>
</tr>
<tr>
<td>( v_T ) ( \pm SE )</td>
<td>21.08 ( \pm 0.94 )</td>
<td>21.64 ( \pm 0.97 )</td>
<td>20.30 ( \pm 1.51 )</td>
<td>14.83 ( \pm 1.32 )</td>
</tr>
<tr>
<td>( v_L \cdot v_T ) ( \pm SE )</td>
<td>2.43 ( \pm 0.15 )</td>
<td>2.32 ( \pm 0.16 )</td>
<td>2.53 ( \pm 0.14 )</td>
<td>2.68 ( \pm 0.14 )</td>
</tr>
</tbody>
</table>

\(^a\)First \( n \) value applies to the first ischemic period and the second applies to the second. Significance difference between mean values at time 0 and during ischemia: \(^b\) \( p < .05 \); \(^c\) \( p < .01 \).

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**FIGURE 2.** Values for \( v_L \) and \( v_T \) and the ratio \( v_L \cdot v_T \) at different times after interruption of coronary flow (global ischemia). Single points indicate mean values and bars indicate standard error. **Left.** First ischemic period; **right.** second ischemic period.
TABLE 1
(Continued)

<table>
<thead>
<tr>
<th>Time after onset of ischemia (min)</th>
<th>Cycle length (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td></td>
</tr>
<tr>
<td>(n = 6; n = 8)</td>
<td></td>
</tr>
<tr>
<td>$V_L$</td>
<td>$V_T$</td>
</tr>
<tr>
<td>33.33</td>
<td>13.00</td>
</tr>
<tr>
<td>3.86</td>
<td>1.15</td>
</tr>
<tr>
<td>c</td>
<td>c</td>
</tr>
<tr>
<td>37.75</td>
<td>13.88</td>
</tr>
<tr>
<td>3.20</td>
<td>1.65</td>
</tr>
<tr>
<td>c</td>
<td>c</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

There was an increase in stimulus interval immediately restored elliptic spread, which then occurred at $V_L = 26$ cm/sec and $V_T = 9$ cm/sec. During regular elliptic spread and during the transition to complete inexcitability no significant shifts in the TQ segment of the DC electrograms occurred. This indicated absence of local differences in resting membrane potentials under the recording electrode.11

The dependence of $V_L$ and $V_T$ on $[K^+]_o$. In 10 of the 16 experiments $[K^+]_o$, concentration was measured close to the multiterminal electrode during ischemia and during normoxic perfusion at elevated $[K^+]_o$ to assess the contribution of its accumulation to conduction slowing during ischemia. The measurements of $V_L$ and $V_T$ were arranged in different groups, each including the values recorded at increments of 2 mM of $[K^+]_o$. The number of experiments resulting in a given range of $[K^+]_p$, and the values for $V_L$, $V_T$, and $[K^+]_o$ are listed in Table 2 and illustrated in Figure 5. During ischemia, the relationship between $V_L$, $V_T$, and $[K^+]_o$, was assessed during the second ischemic period. The results demonstrate a distinct difference between the conditions of ischemia and high-$[K^+]_o$ perfusion. During normoxic perfusion with different concentrations of $[K^+]_p$, a small increase in $V_L$ and $V_T$ occurred on an increase in $[K^+]_o$, to 6 to 8 mM and marked conduction slowing occurred above a mean $[K^+]_o$ of 8.94 mM. At above 14 mM of $[K^+]_o$, the hearts were inexcitable on local stimulation. In contrast, conduction slowing was observed at lower concentrations of $[K^+]_o$ during ischemia. At between 8 to 10 mM $[K^+]_o$, $V_L$ and $V_T$ decreased to approximately 30 and 15 cm/sec. Inexcitability developed at below 11 mM $[K^+]_o$. During perfusion at an elevated $[K^+]_o$ a transitional phase with incomplete spread from the

![FIGURE 3](http://circ.ahajournals.org/) Epicardial activation during global ischemia after central stimulation. Isochrones indicate increments of 10 msec. A, Isochronal map measured 4 min after interruption of coronary flow. Regular elliptic spread ($V_L = 30$ cm/sec; $V_T = 15$ cm/sec). B, Activation pattern after 5 min. Excitation and propagation initially only occurs in longitudinal direction toward the left and in transverse direction toward the lower part of the map. The shadowed area is excited with a delay by circulating excitation as well as by propagation from deeper tissue layers, as indicated by the epicardial breakthrough at 80 msec. Longitudinal velocity on the left part of the axis is 20 cm/sec.
Central electrode developed that was similar to that noted during ischemia (figure 3).

Conduction velocities and resting membrane potentials of propagating slow responses and during ischemia. It has been shown that cardiac impulses may be conducted at velocities of only a few centimeters per second if the regenerative inward current is flowing through slow channels in the absence of a rapid Na⁺ inward current. The term “very slow conduction” was introduced to denote velocities below 10 cm/sec. During ischemia observed conduction velocities in the longitudinal direction were always distinctly higher than this value, whereas transverse conduction decreased toward, or in two experiments was below, 10 cm/sec.

In six hearts so-called slow responses were produced by adding epinephrine (2.5 × 10⁻⁴M) to a perfusate containing 17 to 21 mM [K⁺] to allow comparison of propagation during ischemia with propagation of a slow response. In four hearts transmembrane potentials were measured close to the multiterminal electrode. In all experiments, the ventricular myocardium was inexcitable above 14 mM [K⁺]. Excitability to central stimulation (and spontaneous activity) was restored only after addition of epinephrine.

**TABLE 2**

Relationship between \( v_L \) and \( v_T \) (cm/sec) and [K⁺] (mM) during ischemia and perfusion at elevated [K⁺].

<table>
<thead>
<tr>
<th>Ranges of [K⁺] (mM)</th>
<th>( [\text{K}^+]_o )</th>
<th>( v_L )</th>
<th>( v_T )</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.1–6.0 (n = 19; n = 9)</td>
<td>4.91</td>
<td>54.48</td>
<td>23.26</td>
</tr>
<tr>
<td>6.1–8.0 (n = 11; n = 7)</td>
<td>6.69</td>
<td>40.00</td>
<td>16.46</td>
</tr>
<tr>
<td>8.1–10.0 (n = 6; n = 5)</td>
<td>9.13</td>
<td>32.57</td>
<td>14.57</td>
</tr>
<tr>
<td>10.1–12.0 (n = 8)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ischemia</th>
<th>Mean ( \pm SE )</th>
<th>Mean ( \pm SE )</th>
<th>Mean ( \pm SE )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( [\text{K}^+]_o )</td>
<td>4.91</td>
<td>54.48</td>
<td>23.26</td>
</tr>
<tr>
<td>( v_L )</td>
<td>6.69</td>
<td>40.00</td>
<td>16.46</td>
</tr>
<tr>
<td>( v_T )</td>
<td>9.13</td>
<td>32.57</td>
<td>14.57</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Perfusion at elevated ( [\text{K}^+]_o )</th>
<th>Mean ( \pm SE )</th>
<th>Mean ( \pm SE )</th>
<th>Mean ( \pm SE )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( [\text{K}^+]_o )</td>
<td>4.73</td>
<td>56.22</td>
<td>24.44</td>
</tr>
<tr>
<td>( v_L )</td>
<td>7.41</td>
<td>61.57</td>
<td>24.57</td>
</tr>
<tr>
<td>( v_T )</td>
<td>8.94</td>
<td>49.20</td>
<td>21.60</td>
</tr>
</tbody>
</table>

\(^{a}\)First n values refers to the ischemic condition and the second to perfusion.

Significant differences between mean values at \( [\text{K}^+]_o = 4.1 \) to 6.0 mM and mean values at higher \( [\text{K}^+]_o; \) \(^{b}p < .01.\)
FIGURE 5. Comparison of $v_L$ and $v_T$ during ischemia (closed circles) and during perfusion at elevated concentration of $[K^+]_0$ (open circles). Conduction velocities are plotted vs. $[K^+]_0$ concentration (mean values; bars = SE). Note that slowing of conduction during ischemia occurs at a lower $[K^+]_0$ than it does during perfusion with elevated $[K^+]$.

Figure 6 shows the comparison of an isochronal map obtained during slowed propagation in ischemia with an isochronal map during propagation of a slow response. In this experiment $v_L$ and $v_T$ of the slow response were 12 and 5 cm/sec, respectively, i.e. 57% and 50% of the lowest values recorded during ischemia before the occurrence of inexcitability. The mean velocities calculated from activation patterns in six hearts were (cm/sec, ± SE) $v_L = 12.33 ± 1.23$ and $v_T = 5.00 ± 0.26$ at a mean $[K^+]_0$ of 19.30 ± 0.70 mM (table 3A). These values were distinctly lower than the values recorded during ischemia before the development of inexcitability. Furthermore, the slow responses showed a very long recovery from previous excitation. This is indicated by the long stimulus interval (mean 1533 msec) needed to elicit propagated spread (table 3A). Shortening of this interval was always followed by the occurrence of 2:1 block. The different ionic nature of the propagated responses during ischemia and during perfusion with 20 mM $[K^+]_0$ and epinephrine was indicated by the values of resting membrane potentials measured under the different conditions (table 3B). As shown in figure 7, resting membrane potentials changed from −89 mV during normal perfusion to −58 mV after 7 min of ischemia, when the impaled cell became inexcitable. In the same heart, the ventricular myocardium was inexcitable during perfusion with 21.7 mM $[K^+]$ and a resting potential of −52 mV. Addition of epinephrine restored activity at the same resting membrane potential. In three experiments the mean resting membrane potential at which inexcitability occurred during ischemia was significantly more negative than mean resting membrane potential of propagating slow responses.

![Ischemia 4min 10sec](image1)

![Perfusion, $[K^+]_0 = 19$ mM, Adrenaline](image2)

**TABLE 3A**

| Slow responses: characteristics of conduction (n = 6 experiments) |
|---------|--------------|-------------|-------------|-------------|
| $[K^+]_0$ (mM) | $v_L$ (cm/sec) | $v_T$ (cm/sec) | $v_L / v_T$ | Epinephrine $[K^+]$ (mM) | $10^{-5}$M |
| Mean | 1533 | 12.33 | 5.00 | 2.32 | 19.30 |
| ± SE | 256 | 1.23 | 0.26 | 0.29 | 0.76 |

**TABLE 3B**

| Resting potentials (RMP): ischemia (inexcitability) vs perfusion with high $[K^+]$ and epinephrine |
|---|---|---|---|
| Ischemia (inexcitability) | Slow response |
| $[K^+]_0$ (mM) | RMP (mV) | $[K^+]_0$ (mM) | RMP (mV) |
| Mean | 11.10 | 60.30 | Mean | 20.18 | 48.50 |
| ± SE | 1.00 | 1.45 | ± SE | 0.98 | 2.87 |

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not observed in all experiments. Several factors may account for this finding. Kagiyama et al.21 have shown that acidification of the extracellular space reduces the accelerating effect of a moderate increase in [K+] on conduction. Thus, differences in the development of intracellular and extracellular acidification in our experiments could partially explain the initial variability of \( v_l \) and \( v_T \). In addition, some variation might be related to the limitations of our method. The accuracy of our conduction velocity measurements was limited by the digital sampling rate of 1/msec. This must be taken into consideration when small differences in activation times (i.e., high conduction velocities) are measured, whereas it is of minor importance when propagation is slow.

Slowing of conduction during ischemia was characterized by a fast decrease in \( v_l \) and \( v_T \). Our results did not allow us to distinguish between the changes in different electrical parameters that theoretically may decrease conduction velocity, such as changes in extracellular and intracellular resistances and in action potential generation. A 1.7-fold increase in intracellular longitudinal resistance (or coupling resistance \( r_c \)) was reported after 30 min of myocardial hypoxia.24 During ischemia, when no measurements of \( r_c \) are available, a similar change would, in the case of a uniform cable, decrease conduction velocity by 23%.25 The marked decrease in the amplitude and rate of rise in the action potential during ischemia, which has been observed by several investigators, certainly plays an important role in conduction slowing. During ischemia recovery from inactivation becomes markedly prolonged.13 The refractory period may exceed the duration of the action potentials and amount to several hundred milliseconds. This prolongation most probably was responsible for the occurrence of 2:1 block before total inexcitability.

The incomplete spread from the central stimulus electrode, which occurred before total inexcitability, as shown in figures 3 and 4, was a time-dependent phenomenon. This indicated that all of the tissue was potentially able to conduct the impulse provided that enough time was allowed at a certain site for recovery from the previous inactivation. Some degree of spatial nonuniformity of recovery of excitability is a feature of normal ventricular and atrial muscle.25, 26 Also, it has been shown that several interventions, such as stimulation of the cardiac sympathetic nerves, administration of ouabain, myocardial ischemia, and hypothermia increase local disparity of refractory periods.28 The time dependence of recovery from inactivation in hypoxic myocardium at elevated concentrations of \( [K^+]_o \), is

![FIGURE 7. Recordings of transmembrane potentials during ischemia (top) and during perfusion at different \([K^+]_o\) (bottom). During ischemia only a very small amplitude action potential was present after 7 min at a resting potential (RMP) of \(-58\) mV and \([K^+]_o\) of 9.1 mM. During perfusion with elevated \( K^+ \) inexcitability occurred at above \( 13.9 \) mM [K+] in this experiment. At 21.7 mM [K+] and an RMP of \(-52\) mV the heart was excitable only after administration of epinephrine.](http://circ.ahajournals.org/)

Discussion

The dependence of conduction velocity on cardiac fiber orientation in atrial and ventricular tissue has been demonstrated by many investigators.13, 14 Therefore, quantitative assessment of conduction velocity during the acute phase of myocardial ischemia implied an experimental arrangement in which the influence of fiber direction had to be considered. The values for \( v_l \) and \( v_T \) (cm/sec; mean ± SE) that we obtained on the epicardial surface of the isolated perfused pig heart were \( 50.08 \pm 2.13 \) and \( 21.00 \pm 0.94 \), respectively, before the first ischemic period and \( 50.00 \pm 2.87 \) and \( 21.14 \pm 0.97 \), respectively, before the second ischemic period. These compare favorably with the values (cm/sec) of 58 (\( v_l \)), 28 (\( v_T \))15 and 60 (\( v_l \)) and 28 (\( v_T \))16 measured in the canine epicardium in situ and with the values of 50 (\( v_l \)) and 19 (\( v_T \)) measured in the isolated canine papillary muscle.17

In acute ischemia an initial increase and a subsequent decrease in conduction velocity is suggested qualitatively from measurement of epicardial activation times10 or by the width of the ventricular complex on the extracellular electrogram.20 This initial increase has been related to accumulation of \([K^+]_o\) since a similar effect had been shown in canine Purkinje fibers21 and in canine and guinea pig papillary muscle22, 23 on elevation of \([K^+]_o\) to levels of between 7 and 9 mM. It was attributed to a decrease in the amount of depolarization and charge necessary to reach threshold for rapid Na+ current in cells moderately depolarized by K+. In the present experiments a considerable variability existed, i.e., an initial increase in \( v_l \) and \( v_T \) was.
markedly sensitive to small changes in resting membrane potential. Therefore, small local gradients in resting potential and \([K^+]_o\), could explain the marked spatial nonuniformity observed in the present experiments.

Our results provide two arguments indicating that local differences of resting potential are not required to explain the incomplete spread from the central electrode. First, no significant local TQ segment shifts were recorded, indicating the absence of local gradients in resting potential. Such shifts occur during regional ischemia as a consequence of flow of injury current between regions of different membrane potential. Second, the same pattern of incomplete spread was observed during perfusion with elevated \([K^+]_o\), when \([K^+]_o\) gradients were absent. Also, other reports have indicated a homogeneous distribution of resting potential and \([K^+]_o\) during global ischemia in adjacent subepicardial zones. A possible explanation for nonuniform spatial recovery of excitability was given by Cranefield. The stimulatory efficacy of local current delivered by an extracellular electrode or a propagating wave front is likely to be influenced by the microscopic fiber architecture, i.e., by divergence and convergence of fibers. In tissue of diminished excitability its excitatory effect might become direction dependent at such sites.

**Relationship between accumulation of \([K^+]_o\) and conduction velocity.** Conduction velocities \(v_L\) and \(v_T\) were compared with concentrations of extracellular \(K^+\) during ischemia and during perfusion with high \([K^+]_o\) to assess the contribution of \([K^+]_o\) accumulation in ischemia to conduction slowing. The results demonstrated that the changes in propagation during ischemia could not be explained by \([K^+]_o\) accumulation alone. Several causes might account for the faster change in \(v_L\) and \(v_T\) during ischemia. Morena et al. have shown that the amplitude and the rate of rise in the action potential decrease to a greater extent during ischemia than during high-K+ perfusion at comparable \([K^+]_o\) levels. A similar extradepression is observed if ventricular myocardium is perfused at elevated \([K^+]_o\) and low \(P_o\) or superfused with high \([K^+]_o\) and at low \(pH\). The reasons for this additional effect of ischemia on the shape of the action potential remains to be elucidated. Possible causes include a change in kinetic and steady-state characteristics of the Na+ inward current and/or the development of a large K+ leak, as suggested by voltage clamp and K+ efflux measurements in myocardial hypoxia. In addition, an increase in coupling resistance may also contribute to the extra decrease in \(v_L\) and \(v_T\).

Conduction during ischemia vs conduction of a propagating slow response. Conduction velocity is one of the major parameters that determines the size of a reentrant circuit. In early ischemia, circus movement during ventricular tachycardia and ventricular fibrillation shows relatively large diameters of 6 mm or more. Furthermore, circulating excitation is not stable, but it changes its localization from beat to beat. Thus, an original site of block will conduct the impulse at relatively high velocity during the next activation. The same size of circus movement is also found in tachycardias induced in isolated rabbit atria, where conduction velocities of approximately 20 cm/sec can be estimated from the spacing of the isochrones close to the leading circle.

Our results indicate that the large diameters of these circuits, as well as the alternation between block and conduction, is mainly explained by an abrupt transition from relatively fast conduction to inexcitability and by the dependence of this phenomenon on the interval between two activations. The lowest values for \(v_L\) and \(v_T\) during ischemia were on the order of 20 and 10 cm/sec, respectively. An abrupt transition was also suggested by the observation that a change in cycle length reestablished conduction at previously unresponsive sites with relatively high \(v_L\) and \(v_T\) (figure 4). In contrast, conduction velocities below 10 cm/sec (very slow conduction) have been measured for longitudinal propagation of action potentials carried by the slow inward current. In our experiments, conduction by so-called slow responses was elicited by addition of epinephrine to inexcitable hearts perfused with 20 mM \([K^+]_o\). A partial contribution of the rapid Na+ current to the upstroke of these action potentials was unlikely because they took off from a resting potential (~48.5 mV) at which the rapid Na+ inward current is inactivated. The velocities for longitudinal and transverse spread of a slow response were distinctly lower than the lowest values measured during ischemia.

Two conclusions are suggested from our comparison of \(v_L\) and \(v_T\) during ischemia with propagation of a slow response: First, \(v_L\) and \(v_T\) during acute ischemia are significantly higher than conduction velocities of a slow response. During ischemia the limit for very slow conduction is reached only in the transverse direction. Second, the depressed action potentials in acute ischemia seem to be initiated by the rapid Na+ inward current. This is suggested by the observation that membrane responses in acute ischemia are abolished at mean resting potentials more positive than ~60.33 mV (table 3B) and by the depressing effect of lidocaine on these action potentials.
References

Changes in conduction velocity during acute ischemia in ventricular myocardium of the isolated porcine heart.
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