Effects of Some Components of Ischemia on Electrical Activity and Reentry in the Canine Ventricular Conducting System

JOCHEN SENGES, JOHANNES BRACHMANN, DIETER PELZER, TETSUO MIZUTANI, AND WOLFGANG KÜBLER

SUMMARY We used intracellular microelectrodes to study the electrophysiological effects of combinations of components of ischemia and their relation to the occurrence of ventricular arrhythmias in the specialized conducting system of isolated canine right ventricles. The middle area of the free wall was exposed to various test solutions in the center compartment of a three-chambered bath; the base and apex of the preparation were superfused with normal Tyrode’s solution in the outer control compartments. Hypoxia (Po2 40 mm Hg), lactic acidosis (pH 6.5), and orciprenaline (10⁻⁴ M), either alone or combined, failed to affect the action potential amplitude or the conduction velocity of the subendocardial fibers, and no arrhythmias occurred. The action potential duration and the effective refractory period were markedly prolonged by lactic acidosis. Exposure of the test regions to 15 mM K+ plus orciprenaline resulted in marked decreases in action potential amplitude and conduction velocity. Abnormalities of impulse transmission through the depressed area included high degrees of rate-dependent block, one-way block, warming-up phenomenon, and the Wenckebach phenomenon. Such conditions regularly provoked the appearance of single, sustained, or concealed reentrant depolarizations. The combined effects of hypoxia, 15 mM K⁺, and orciprenaline resulted in further depression of the already depressed action potential in the depolarized fibers. Our results indicate that regional increases of extracellular K⁺ may be the predominant factor of the components of ischemia we studied which facilitates the initiation of reentrant arrhythmias.

THE MECHANISM for early ischemic arrhythmias appears to depend on the effects of such components of myocardial ischemia as hypoxia, anaerobic metabolites, pH changes, K⁺, catecholamines, and adenosine on the electrical properties of cardiac fibers (Wit and Bigger, 1975; Opie et al., 1973; Downar et al., 1977). Hypotheses concerning possible characteristics of electrical activity in ischemic or infarcting myocardium can be derived from results of electrophysiological studies on isolated, superfused cardiac tissues exposed to such substances as may be present in the ischemic environment. Most studies on the effects of components of ischemia on cellular electrical activity have been performed using single substances (Trautwein et al., 1954; Fozzard, 1975; Brown and Noble, 1972; Antoni and Zerweck, 1967; Cranefield et al., 1971). However, the effects of the combination of agents present during ischemia may not be entirely predictable from our knowledge of the effects of individual components. Information on the electrophysiological effects of combinations of different substances present in and around infarcts is still inadequate.

The majority of knowledge about cellular electrical events accompanying cardiac ischemia is derived from experimental models in which the tissue was uniformly exposed to ischemic components throughout its length (Downar et al., 1977; Wännemark et al., 1968; Pappano, 1970; Carmeliet and Vereecke, 1969; Trautwein and Schmidt, 1960; Engstfeld et al., 1961). A series of very interesting studies by Cranefield et al. reported the development of a remarkable model for the abnormal conduction which might exist in clinical arrhythmias associated with myocardial infarction (Cranefield et al., 1971; Cranefield and Hoffman, 1971; Cranefield et al., 1972). This experimental preparation is represented by a bundle of Purkinje fibers with a segment of depressed excitability intervening between two segments of normal tissue. In these studies, the depressed center segment was subjected to high K⁺ and epinephrine. No other combinations of components of ischemia were studied. In the present experiments, this technique was extended to large strips of the canine ventricle, using a three-chamber method for regional superfusion of the ischemic area surrounded by normal myocardium. This permitted the recording of transmembrane action potentials at each end and within the "is-
chemic" area. The purpose of the present experiments was to study, first, the electrophysiological effects of combinations of hypoxia, lactic acidosis, catecholamines, and high K⁺ and, second, the relations between these regionally induced effects and the occurrence of ventricular arrhythmias.

**Methods**

Mongrel dogs were anesthetized with sodium pentobarbital (30 mg/kg, iv). The chest was opened and the heart quickly excised and placed in cool, oxygenated Tyrode's solution. The free wall of the right ventricle was dissected free by parallel cuts extending from the atrioventricular groove to the right ventricular apex. The epicardial one-third of the preparation then was removed to facilitate the mounting of this tissue block in the perfusion chamber. During removal of the epicardium, care was taken to avoid touching the endocardial surface. The dimensions of the ventricular strip were about 6 x 4 x 0.3 cm. The preparation was pulled through closely fitting holes in two rubber membranes which divided the 50-ml Perspex tissue bath into three compartments. The width of the middle compartment was 2 cm. The holes were individually adjusted to each preparation to avoid injury of the endocardium by the rubber membranes. By this procedure a rather good separation between the perfusion solutions of the three chambers could be obtained, as shown by selective perfusion of each chamber with methylene blue at the end of the experiments.

The preparation then was pinned (with the endocardial surface upward) to the waxed base of the bath and the three compartments were perfused at a rapid rate (30 ml/min) with modified Tyrode's solution of the following composition in mM (Brengman et al., 1969): NaCl, 107.7; KCl, 3.48; CaCl₂, 1.53; MgSO₄, 0.68; NaHCO₃, 26.2; NaH₂PO₄, 1.67; Na gluconate, 9.64; glucose, 5.55; and sucrose, 7.6. The solution was equilibrated with a mixture of 95% O₂-5% CO₂. Temperature was maintained constant at 36.5 ± 0.5°C.

Changes of regional ventricular perfusion were simulated by perfusion of the middle compartment with different test solutions while the outer compartments were continuously perfused with normal Tyrode's solution. The following test solutions were used: (1) Hypoxic Tyrode's solution of normal composition but equilibrated with a mixture of 95% N₂-5% CO₂. Measurements of PO₂, PCO₂, and pH were made by withdrawing samples of Tyrode's solution from each compartment and analyzing them with a pH/gas analyzer (Radiometer, Copenhagen). The PO₂ fell from 460 ± 20 to 40 ± 10 mm Hg within 15 minutes; pH (7.4 ± 0.04) and PCO₂ (40 ± 2.1 mm Hg) remained unchanged in all three compartments. (2) Lactic acidosis was produced by addition of small amounts of 1M lactic acid to the Tyrode's solution buffered with Tris (pH 7.4 ± 0.04 to 6.5 ± 0.09) (3) Tyrode's solution containing 15 mM K⁺; and (4) Orciprenaline at 10⁻⁶ M concentration. The effects of these four components of ischemia—hypoxia, lactic acidosis, high extracellular K⁺, catecholamines—on the electrophysiological parameters were studied either alone or in combination.

For antegrade and retrograde conduction, the isolated myocardium was stimulated through bipolar silver electrodes placed on Purkinje fibers near the ventricular apex or in the basal region. Impulse propagation from apex to base was defined as antegrade. Stimuli were rectangular pulses (2 msec in duration and twice threshold voltage) generated by a Grass pulse generator and passed through an isolation transformer. To determine the effect of test solutions on intraventricular conduction as a function rate, antegrade and retrograde stimulation was performed at decreasing cycle lengths until some impulse failed to conduct through the area located in the middle compartment. The effect of the test solutions on the effective refractory period of the ventricular specialized conducting system was determined at a constant ventricular cycle length (1000 msec). Premature stimuli of 4 times rhoebasic strength and 2-msec duration were introduced after every eighth basic drive stimulus. The antegrade effective refractory period of the ventricular specialized conducting system was defined as the shortest S₁-S₂ interval of stimuli applied to the apical control area at which the premature ventricular response still conducted through the test area to the opposite control area. Transmembrane action potentials were recorded simultaneously from three sites in each outer region and one in the middle test region. At each site, action potentials were recorded only from the most superficial subendocardial fibers. At most recording sites, these subendocardial action potentials were typical for Purkinje fibers and, less frequently, action potentials with characteristics of ventricular muscle fibers were observed. However, the identification of Purkinje fiber action potentials was not confirmed by measuring the maximal rate of depolarization. The depth of the fluid over the preparation was maintained at minimal level to minimize unwanted capacitance in the recording system due to the topography of the preparation. Action potential amplitude and repolarization time to 95% were measured. Intraventricular conduction time was determined as the interval between the upstrokes of action potentials recorded from fibers in the ventricular basal and apical regions. To evaluate conduction velocity, the distance between the respective fibers was measured. Electrophysiological-histological correlation studies in similar ventricular preparations have shown that normal transmembrane action potentials can be recorded as deep as 15–20 fibers beneath the endocardial surface corresponding to histologically normal-appearing tissue throughout the entire thickness of the ventricular strips (Friedman et al., 1973).
Under control conditions, rapid spontaneous activity never occurred for more than several minutes after the preparation were mounted in the tissue bath. Therefore, the preparations could be driven at a very low rate (from 30/min to as low as 6/min). This made it easy to turn off the drive in time to prevent the next stimulus from interrupting an arrhythmia when one appeared; it also served as a check on the absence of spontaneous activity.

Results

Effects of Regional Hypoxia, Acidosis, and Orciprenaline

The effects of different combinations of regional lactic acidosis, hypoxia, and orciprenaline on the ventricular conducting system are illustrated in Figure 1. Action potential amplitude showed no significant variation in the different anatomical areas. Table 1 presents control values of the action potential parameters of superficial subendocardial fibers in the right ventricular free wall and compares them with similar measurements after 1 hour of regional superfusion of the middle area with various test solutions. Regional hypoxia, lactic acidosis, and orciprenaline alone or in combination induced no significant changes of the action potential amplitude. Concomitantly, the ventricular conduction velocity was not significantly altered (Table 1). Also, the critical cycle length at which with increasing stimulation rate ventricular conduction block first occurred did not significantly change in presence of either test solution (Table 1).

The action potential duration showed significant variation in different regions of the preparation under control conditions. Areas of maximal action potential duration were consistently found in the middle region of the free wall. Although this made it difficult to compare analogous regions of different preparations, such a comparison was attempted for subendocardial fiber action potential durations at the middle region of the right ventricular free wall. The results are shown in Table 1. During 1 hour of regional hypoxia, there was a modest shortening of the action potential in the middle area which failed to become significant when all results were summarized because of the large standard deviation. Concomitantly, the effective refractory period for

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Effects of Regional Hypoxia (Po2 40 mm Hg), Lactic Acidosis (pH 6.5), and Orciprenaline (10^-8 M) on Electrical Parameters of the Right Ventricular Conducting System</th>
</tr>
</thead>
<tbody>
<tr>
<td>Free wall</td>
<td>n</td>
</tr>
<tr>
<td>Control</td>
<td>6</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>6</td>
</tr>
<tr>
<td>Control</td>
<td>6</td>
</tr>
<tr>
<td>Acidosis</td>
<td>6</td>
</tr>
<tr>
<td>Control</td>
<td>4</td>
</tr>
<tr>
<td>Hypoxia + acidosis</td>
<td>4</td>
</tr>
<tr>
<td>+ orciprenaline</td>
<td></td>
</tr>
</tbody>
</table>

Data were obtained in three-chamber experiments and were determined 1 hour after addition of the respective test solution to the center area. Stimulation rate, 60/min; n, number of experiments; APA, action potential amplitude recorded from subendocardial fibers at the center test area (ventricular free wall); APD, action potential duration; A, antegrade conduction; CV, conduction velocity; ERP, effective refractory period; CLVA, cycle length at which ventricular block first occurred; Ar, incidence of arrhythmias. Results are expressed as means ± SEM. Significance P of the difference of means between the respective control and test values was determined by Student's t-test.

* P < 0.05 from the control value.
propagation of antegrade or retrograde premature impulses remained unchanged.

Lactic acidosis markedly increased the action potential duration in the test area and led to a significant prolongation of the effective refractory period (Table 1). These effects were most pronounced at low stimulation rates and gradually disappeared with decreasing cycle length (Fig. 2), resulting in only little prolongation of the action potential duration caused by acidosis at high stimulation rates (Fig. 1). In the outer control areas, only a small increase in action potential duration from 245 ± 45 to 275 ± 55 ms (90/min stimulation rate) was observed which was probably related to leakage of the acid test solution into the outer control compartments.

During regional hypoxia or lactic acidosis, no arrhythmias were observed. In the presence of orciprenaline and normal potassium concentrations, occasional slow spontaneous rhythms associated with spontaneous diastolic depolarizations occurred. These were suppressed at a stimulation rate of 30/min.

### Table 2: Effects of Regional High K⁺ (15 mM) in Various Combinations with Orciprenaline (10⁻⁶ M) and Hypoxia (Pₒ₂ 40 mm Hg) on Electrical Parameters of the Right Ventricular Conducting System

<table>
<thead>
<tr>
<th></th>
<th>Basis APA (mV)</th>
<th>Free wall APA (mV)</th>
<th>Apex APA (mV)</th>
<th>CVₐ (m/sec)</th>
<th>CVᵣ (m/sec)</th>
<th>Ar.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>n = 12</td>
<td>110 ± 9</td>
<td>120 ± 11</td>
<td>110 ± 11</td>
<td>1.3 ± 0.25</td>
<td>1.3 ± 0.25</td>
</tr>
<tr>
<td>15 mM K⁺</td>
<td>12</td>
<td>110 ± 14</td>
<td>0*</td>
<td>100 ± 16</td>
<td>0*</td>
<td>0*</td>
</tr>
<tr>
<td>15 mM K⁺</td>
<td>9</td>
<td>100 ± 18</td>
<td>60 ± 18*</td>
<td>98 ± 21</td>
<td>0.55 ± 0.25*</td>
<td>0.32 ± 0.15*</td>
</tr>
<tr>
<td>+ orciprenaline</td>
<td>6</td>
<td>100 ± 16</td>
<td>45 ± 10†</td>
<td>96 ± 27</td>
<td>0*</td>
<td>0*</td>
</tr>
</tbody>
</table>

Data were obtained in three-chamber experiments and were determined 15-30 minutes after the addition of the respective test solution to the center compartment. Stimulation rate, 20/min; n, number of experiments; APA, action potential amplitude recorded from subendocardial fibers at the basal control area, center test area (ventricular free wall), and apical control area; CV, conduction velocity; A, antegrade; R, retrograde; B, block of conduction; Ar., incidence of arrhythmias. Results are expressed as means ± SD. Significance was tested by Friedman's test (Immich, 1974). The decrease in APA at the base and at the apex in rows 3 and 4 is probably related to leakage of K⁺ into the outer control compartments.

* P < 0.01; † P < 0.05.

**Figure 2** Effect of regional acidosis (pH 6.5; middle trace) on action potential duration of a subendocardial fiber at increasing ventricular rates (30-240/min). Top and bottom traces are controls. The asynchronous depolarization of action potentials in the lower trace is caused by increasing latency at rapid stimulation rates.

**Figure 3** Effect of regional high K⁺ and orciprenaline on the ventricular conducting system. In each panel, top and bottom traces are controls. The middle trace shows records from the same fiber within the center area superfused with the following test solutions: top panel, normal Tyrode's solution; left and middle bottom panel, Tyrode's solution containing 15 mM K⁺ for 2 minutes and for 6 minutes; right bottom panel, Tyrode's solution containing 15 mM K⁺ plus 10⁻⁶ M orciprenaline for 10 minutes. Stimulation at the basal area (20/min).
and the effective refractory period (ERP) for propagation of premature ventricular impulses varied widely between individual depressed preparations. However, both parameters were markedly prolonged ranging from 600 to 3000 msec (CLVB, n = 9; Fig. 4) and from 250 to 600 msec (ERP, Fig. 10; for control values see Table 1).

Unidirectional block of conduction within the depressed area of the test compartment was often observed at decreasing cycle lengths. In addition, significant differences in the prolongation of ventricular conduction time occurred at slow stimulation rates depending on the site of impulse initiation (Table 2). Antegrade propagation of impulses was less inhibited than retrograde conduction favoring propagation of excitation initiated within the ventricular apex.

Regional depression of excitability induced by high K* and orciprenaline provoked regularly the appearance of return extrasystoles. On the contrary, pacemaker activity dependent on diastolic depolarization or on oscillatory after potentials was never observed in the presence of 15 mM K+ plus 10^-6 M orciprenaline. A typical example of apparent reentrant excitation is illustrated in Figure 5. The stimulus artifacts in all records have been intensified to make clear which action potentials were evoked by applied stimuli and which were spontaneous. In this preparation, the recording site in the middle compartment was closer to the apical area, resulting in different responses to antegrade and retrograde impulse propagation probably because of decremental conduction within the depressed area.

Figure 5 (left) shows that a single stimulus applied to the base of the ventricle is followed at the transmission of the driven impulse does a return extrasystole at the stimulation site. Top and bottom traces are spontaneou
However, with every successive beat, the amplitude of the local response steadily increased. This increase did not result from an alteration in the timing of stimulation but rather from some "warming-up" of responsiveness in the depressed area. When the local response became suprathreshold and the impulse was conducted to the apical area, a reentrant excitation was initiated.

In the experiment shown in Figure 6, conduction through the depressed area was completely blocked in both directions by increase in the stimulation rate. However, re-excitations could be initiated at antegrade and retrograde stimulation sites even in the absence of forward transmission. Only one action potential was conducted into the middle of the depressed area, suggesting that the reentrant pathways were localized near the junction between the test compartment and the respective outer control area.

Slowing and block of conduction within the depressed region were strikingly sensitive to rate. When the driving rate was abruptly increased from 90 to 180/min, the fibers of the depressed region showed only small depolarizations, and there was no spread of excitation to the opposite control area. This block of the response persisted until rapid stimulation was terminated. Moderate rates facilitated the appearance of slow conduction showing the Wenckebach phenomenon. The 3:2 phase of the block in the left panel of Figure 7 shows the Wenckebach phenomenon of delay, greater delay, and a dropped impulse.

Since reentry was found to depend on delay, the effects of rate on re-excitation also were studied. The records in Figure 8 were obtained from a preparation demonstrating reentrant excitation of the stimulation site at the ventricular apex (lower trace) in the absence of impulse transmission to the ventricular base (upper trace). At a rate of 60/min, most driven impulses were propagated to the depressed region (middle trace) and were followed by a second normal action potential at the stimulation site. One impulse was blocked at a more apical site and no return extrasystole occurred. When the rate was 60/min 70/min 85/min 100/min

**Figure 6** Effect of blocked forward transmission on reentry within a depressed area. The top and bottom traces are controls. The middle trace was obtained from the depressed center area superfused with Tyrode's solution containing 15 mM K⁺ plus 10⁻⁶ M orciprenaline; stimulation rate, 20/min. In the left panel, the basal end was stimulated. The driven impulse reaches the depressed site with marked delay and further transmission to the apical control area is blocked, but a second normal action potential is initiated at the stimulation site. In the right panel, the apical end was stimulated showing also block of forward transmission but re-excitation of the stimulation site.

**Figure 7** Effect of hypoxia on slow conduction showing the Wenckebach phenomenon within a depressed area. Top and bottom traces are controls. The middle trace was obtained from the depressed center area superfused with Tyrode's solution containing 15 mM K⁺ plus 10⁻⁶ M orciprenaline before (left panel) and 30 minutes after oxygen deficiency (Po₂ 40 mm Hg, right panel); stimulation rate, 60/min. In the left panel, depressed conduction shows a 3:2 Wenckebach cycle. Hypoxia markedly exaggerates the depression of electrical activity within the center area, showing small depolarizations and high degree block.

**Figure 8** Effect of ventricular rate on reentry within a depressed area. In each panel, top and bottom traces show membrane potentials recorded from the same fibers in outer control areas, and the middle trace was obtained from the same fiber in the depressed center area superfused with Tyrode's solution containing 15 mM K⁺ plus 10⁻⁶ M orciprenaline. When the apical end is stimulated at rates faster than 30/min, forward transmission to the basal area is completely blocked but conduction in the depressed area still occurs. With increasing rate, the amplitude of the depressed action potential is progressively decreased, and higher degrees of block appear within the depressed region. The complex relationship between ventricular rate and frequency of reentry is discussed in the text. Note stimulus artifacts at the top trace for differentiation of driven and reentrant excitations.
increased to 70/min, 2:1 block appeared, and only every second driven impulse evoked a reentrant excitation. However, with a progressive increase in stimulation rate to 85/min, again every driven action potential was followed by a return extrasystole. Under these conditions, every second drive stimulus fell within the refractory period of the reentrant action potential and failed to initiate an impulse. When the rate was further increased to 100/min, the amplitude of the depressed action potentials markedly decreased, 4:1 block occurred, and reentry almost vanished, resulting in effective initiation of driven impulses by every drive stimulus.

In the presence of regional high K$^+$ plus orciprenaline, premature stimuli could induce both the initiation and the interruption of reentrant excitations. Figure 9 shows that a premature excitation provoked reentry more readily than the regular impulse. In this preparation, two recording sites were directly at the junctions between the depressed center area and the ventricular base (upper trace) or the apical region (lower trace), demonstrating action potentials similar to those obtained within the depressed region (middle trace).

The basic impulse regularly failed to evoke reentry. In the left panel, a premature impulse induced 220 msec after the drive reached the middle of the depressed area but was not propagated to the apical junction. In the right panel, a premature impulse evoked 260 msec after the drive excited a response at the apex with marked delay. This was the condition necessary for establishing a reentrant circus movement. The premature response returned to the middle area and basal junction, effecting full reentry. In addition, all following impulses resulted from reexcitations via sustained circus movements without further applied stimuli. The sequence of impulses was similar to the one provoked by the premature stimulus; the impulse traveled 4 to 6 times around the circuit generating a tachycardia of about 170/min.

In contrast, Figure 10 shows that a premature excitation could also abolish reentry. In this preparation, the driven impulse regularly evoked a reentrant response within the depressed region. However, this second response failed to complete a circus movement and was blocked when it reached the stimulation site that was still refractory. This phenomenon might be called concealed reentry and was observed often. In the left panel, a premature excitation induced 550 msec after the drive was propagated to the apex with rather little increase in delay as compared with Figure 9. However, this premature response was not able to evoke concealed reentry, and no second depolarization occurred at the depressed site. In the right panel, shortening of the coupling interval to 400 msec caused complete block of impulse transmission. In this preparation, the marked prolongation of the effective refractory period associated with only little increase in conduction delay might explain that the premature impulse died out and failed to evoke reentry.

In contrast to the small effect of oxygen deficiency in normal solution, hypoxia significantly antagonized the ability of orciprenaline to restore excitability in K$^+$-depolarized subendocardial fibers. These combined effects are summarized in Table 2 and Typical tracings are shown in Figure 7. The most marked change was a decrease in action potential amplitude resulting in a high degree block of impulse propagation. Reentrant excitations were less frequently observed under these experimental conditions than they were in the absence of hypoxia.
Discussion

In this experimental model, the spatial variability of components of ischemia in and around an infarcted area was imitated by some junctional leakage observed between test compartment and outer control compartments. The method does not, therefore, provide a precise determination of the effect of the agents applied to the middle region of the preparation. However, the spatial variability of the depression reveals the peculiarities of conduction in a ventricular area, the fibers of which are on the border between conduction and block, and thus resemble fibers in the heart that are damaged and are neither normal nor inexcitable (Cranefield et al., 1971). Preliminary studies of ventricular preparations using ion-sensitive microelectrodes revealed no significant leakage of K+ from deeper subendocardial layers to superficial fibers during normal oxygenation and hypoxic conditions (Sonnhof and Senges, unpublished observations).

In the presence of regional high K+ and orciprenaline, the depressed response of subendocardial fibers was characterized by action potentials of low amplitude associated with slow conduction (Cranefield et al., 1972; Wit et al., 1972a; Wit et al., 1972b). Various abnormalities of conduction including higher degrees of rate-dependent block, one-way block, warming-up phenomenon, and Wenckebach phenomenon were regularly seen, confirming the "agar sandwich" studies of Cranefield et al. on small bundles of Purkinje fibers (Cranefield et al., 1971; Cranefield and Hoffman, 1971). However, the combined effects of high K+, catecholamines, and hypoxia have not yet been described. Under these experimental conditions, hypoxia significantly antagonized the ability of orciprenaline to improve depressed electrical activity. It is interesting to note that in isolated rabbit atria, hypoxia predominantly depressed sinoatrial and atrioventricular nodal action potentials dependent on slow response activity (Senges et al., 1978; Kohlhardt et al., 1977; Wit and Cranefield, 1974). In the absence of high extracellular K+, even combinations of hypoxia plus lactic acidosis plus orciprenaline failed to affect significantly both the amplitude of subendocardial fiber action potentials and ventricular conduction. Similar results have been observed using the same substances individually (Fozzard, 1954; Brown and Noble, 1972; Antoni and Zerweck, 1967; Trautwein and Schmidt, 1960), but the combined effects have not yet been reported.

Regional lactic acidosis markedly prolongs both the action potential duration and the refractory period of subendocardial fibers (Brown and Noble, 1972). Although hypoxia failed to affect significantly these parameters in superficial cells, it is well known that anoxia shortens the refractory period in ordinary ventricular fibers localized within deeper layers (Trautwein et al., 1954; MacLeod and Frasad, 1969). Thus, both lactic acidosis and hypoxia increased the local heterogeneity of refractory periods but failed to facilitate reentry. The important common fact in both components of regional ischemia is that they also failed to cause a conduction delay. Therefore, mere local patches of inhomogeneous refractoriness seem not to make a potent contribution to ventricular reentry, and some degree of local slow conduction also appears to be needed (Cranefield, 1975; Sasy suicide and Mendez, 1971). In the presence of regional high K+ and orciprenaline, full recovery of excitability did long outlast full membrane repolarization, indicating that the refractory period of the depressed fibers was much less dependent on the action potential duration.

In 1972, Wit, Cranefield, and Hoffman (Wit et al., 1972b) clearly stated that it is almost impossible to prove that a sequence of activity that appears to depend on a circus movement of excitation really does depend on such a movement; as with any complex phenomenon, it is always possible to invent alternative explanations. However, it is well known that catecholamines never produce diastolic depolarization in the presence of high K+ (Wit et al., 1972a; Wit et al., 1972b; Vassalle and Barnabel, 1971), and this has been confirmed in the present experiments. The following properties of return excitations were observed: (1) The sequence of activation seen was that expected in a circus movement. (2) This sequence remained the same throughout the apparent circus movement, and activity died out in the correct sequence. (3) Return excitations occurred only in the presence of delay and asymmetry of conduction. This description fits the criteria for accepting circus movement as the basis of repetitive activity (Wit et al., 1972b).

Recent experimental evidence supports the view that reentrant arrhythmias may result from slow conduction through discrete regions of partially depolarized fibers (Cranefield et al., 1971; Cranefield and Hoffman, 1971; Wit et al., 1972a; Wit et al., 1972b). This was confirmed in the present experiments demonstrating a close relationship between slowing of conduction and the occurrence of reentry. Accordingly, hypoxia, lactic acidosis, and orciprenaline—either alone or combined—failed to facilitate reentrant arrhythmias which were observed only after regional increase in K+. Combinations of high K+ with orciprenaline markedly increased the incidence of reentry, whereas it was rather reduced after the addition of hypoxia. This observation implies that, under certain conditions, increasing PO2 may even contribute to the occurrence of reentrant arrhythmias. A recent study (Downar et al., 1977) has reported additional unidentified factors of ischemia which appear to exert a potent depressant effect of the excitability of normal myocardium.

Abnormal conduction through partially depolarized fibers in the presence of high K+ may explain many well known electrocardiographic abnormalities of the rhythm and activation of the heart. The observed single and sustained circus movements
constitute a mechanism by which extrasystoles or moderate ventricular tachycardias may arise. Very rapid rates of sustained reentrant activity were never initiated in the present experiments, indicating that additional factors may be involved in ventricular tachycardias observed in subendocardial Purkinje fibers surviving extensive myocardial infarction (Friedman et al., 1973; Lazzara et al., 1973). Similar to clinical observations (Wellens et al., 1974), premature impulses were able to initiate and to interrupt reentrant rhythms. In addition, premature excitation may also undergo concealed reentry. Although this blocked impulse would be electrocardiographically silent, it would alter the conditions for the following excitations in the reentry pathway, facilitating or inhibiting the appearance of extrasystoles.

The relationship between basic rate and the frequency of reentry is not a simple one, and this has been explained by various summation and inhibition phenomena (Cranefield, 1975). In addition, the present results indicate that rate-dependent reentrant excitations may inhibit the basic stimuli to initiate propagated action potentials. Under such conditions, either an increase or a decrease in supraventricular rate may enhance the frequency of ventricular reentry.

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