Reentrant Ventricular Arrhythmias in the Late Myocardial Infarction Period

7. Effect of Verapamil and D-600 and the Role of the “Slow Channel”

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SUMMARY  Reentrant ventricular arrhythmias (RVA) were analyzed in dogs 3–7 days after ligation of the anterior descending coronary artery using averaged “composite” recordings of electrical activity of reentrant pathways (RP) from the epicardial surface of the infarction zone (IZ). Verapamil (V) and D-600 (D) (0.2–0.5 mg/kg i.v.) resulted in slight-to-moderate improvement of conduction in RP with abolition of spontaneous RVA and RVA initiated by premature depolarizations. The effect of V was not blocked by pretreatment with propranolol (0.5 mg/kg i.v.). Using a standard microelectrode technique and strips of epicardial muscle from the IZ, D (0.5–1 × 10^{-4} g/ml) slightly improved the upstroke velocity and membrane responses of depressed ischemic cells. In contrast, tetrodotoxin (5 × 10^{-4} g/ml) further depressed or abolished action potentials of ischemic cells. We conclude: 1) the moderate antiarrhythmic effect of V and D on RVA is the result of improved conduction in RP; 2) this action is partly explained by improvement of a depressed sodium channel and is not related to catecholamine release; 3) slow-response action potentials play no significant role in the genesis of ischemia-related RVA, which probably results from depression of the fast response.

IN THE LATE myocardial infarction period (3–7 days after infarction), the propensity for reentrant ventricular arrhythmias is still maintained. In a recently described canine model, reentrant ventricular arrhythmias were remarkably stable, and averaged recordings of the electrical activity of reentrant pathways could be obtained from the epicardial surface of the infarction zone with a specially designed composite electrode. The canine model was used in both in vivo and in vitro experiments to study the mechanism of action of lidocaine and dipherelydantoin. Both drugs owed their antiarrhythmic effect to selective prolongation of refractoriness and depression of conduction in reentrant pathways in ischemic myocardium.

In this study, we analyzed the effects of verapamil and its methoxy derivative, D-600, on electrophysiological properties of ischemic myocardium and on related reentrant ventricular arrhythmias in both in vivo and in vitro experiments. The effect of D-600 on ischemic myocardial cells is also contrasted with that of tetrodotoxin. Both verapamil and D-600 are thought to act by blocking the slow inward current carried by calcium (Ca^{2+}) and possibly by sodium (Na^+). It has been suggested that slow conduction in depressed cells, including ischemic myocardium, that can lead to reentrant ventricular arrhythmias is a property of the slow response action potential. This study provides a direct evaluation of the role that the slow-response action potential plays in ischemia-related reentrant ventricular arrhythmias. It also investigates possible ionic conductance abnormalities in ischemic myocardium.

Material and Methods

In Vivo Experiments

Adult mongrel dogs were studied 3–7 days after ligation of the left anterior descending artery just distal to the anterior septal branch. In all dogs, a transmural infarction was evident on gross postmortem examination. Recordings were obtained from the epicardial surface of the infarction zone (IZ) and adjacent normal zone (NZ) with a composite electrode that records averaged signals of multiple close bipolar sites. In every experiment at least a single composite electrogram was recorded from each IZ and NZ. In more than half of the experiments, one to three close bipolar recordings from the IZ and/or NZ were also obtained. Details of the surgical procedure and the recording techniques are described elsewhere. In addition to the electrograms, two standard ECG leads were recorded, leads II and aV_{III}. All recordings were obtained on a multichannel oscilloscopic photographic recorder (E for M, DR-10) at paper speeds of 25–200 mm/sec. Recordings made at 25 mm/sec were used for orientation of the basic cardiac rhythm. Relevant electrophysiologic measurements were always obtained from recordings made at 100–200 mm/sec. ECGs were recorded with the preamplifier set for frequencies of 0.1–200 Hz. Bipolar electrograms were recorded with filter frequencies of either 40–200 or 12–200 Hz. The error in measurement was ± 3 msec at a paper speed of 200 mm/sec.

Dogs were anesthetized with 30 mg/kg i.v. sodium pentobarbital. A jugular vein was cannulated for the administration of fluids. Blood pressure in the femoral artery was monitored through a polyethylene catheter.
connected to a Statham transducer. The sinus node area was either crushed or excised to obtain a slower atrial or atrioventricular (AV) junctional rhythm. Atrial or His bundle pacing was used to control the ventricular rate. Atrial pacing was achieved via two fine stainless steel wires (0.003-inch diameter) inserted through a 25-gauge hypodermic needle into the left atrial appendage. His bundle pacing was done through the same electrodes on the catheter recording the His bundle electrogram. Both regular pacing and premature stimulation were performed using a programmed digital stimulator that delivered rectangular impulses 1.5 msec long at twice diastolic threshold. Refractoriness in the IZ was determined by analysis of the IZ composite electrogram (IZeg) during premature stimulation. Refractoriness was defined by the character of the responses themselves. During a basic driving rate associated with 1:1 response of the IZeg, premature stimuli were delivered every fifth paced beat at gradually shorter coupling intervals. The longest coupling interval that would result in further increase of the duration of the IZeg was defined. This interval is considered to represent the "averaged" relative refractory period of the IZ. Because of the nature of the composite electrode recording, this interval probably only reflects the relative refractory period of the more severely depressed parts of the IZ. However, changes in this interval after drug administration would reflect the effect of the drug on refractoriness in the IZ.

Protocol

In 10 experiments, verapamil (Knoll Pharmaceutical) was administered as a 0.5 mg/kg intravenous bolus injection, and the effect on conduction in the IZ and on reentrant ventricular arrhythmias were continuously monitored in ECG leads and in IZ and NZ electrograms for at least 30 minutes after injection. In seven experiments, the effects of a 0.5 mg/kg intravenous bolus injection of racemic D-600 (α-isopropyl-α (N-methyl-N-homoveratryl)-Y-amino- propyl)-3,4,5-timethoxyphenylacetoniitrile HCl), the methoxy derivative of verapamil (Knoll Pharmaceutical), were analyzed. In some experiments, 45 minutes were allowed for return to control before the effect of another dose of verapamil or D-600 was studied. The above dose of verapamil and D-600 resulted in AV nodal conduction delay and/or AV nodal block at atrial pacing rates lower than control in all experiments. In all but two experiments, we used His bundle pacing to study the effect of short cardiac cycle lengths after injecting verapamil or D-600. In six experiments, the response to a smaller dose of verapamil (0.2 mg/kg) was studied before and after β-adrenoreceptor blockade by propranolol (0.5 mg/kg). This dose of propranolol completely blocked the cardiac effects of isoprenaline (0.1 µg/kg). Results were statistically analyzed with the paired t test.

In Vitro Experiments

Hearts were removed from 12 mongrel dogs 3–7 days after ligation of the anterior descending coronary artery just distal to the anterior septal branch. Preparations containing both normal and ischemic myocardium were dissected from the epicardial surface. The infarcted myocardium was distinguished by its pale and hemorrhagic surface. The preparations were superfused at 35–37°C with a physiologic solution of the following composition (in mM): sodium ion 151.1, potassium ion 4.05, calcium ion 1.35, magnesium ion 0.5, chloride ion 131.25, bicarbonate 24.0, diibasic phosphate 1.8, and dextrose 5.5. D-600 was added to the superfusate in concentrations of 0.5 × 10⁻⁶ g/ml or 1 × 10⁻⁶ g/ml. In six preparations, we analyzed the effect of tetrodotoxin (5 × 10⁻⁴ g/ml). After return to control, these preparations were subsequently exposed to D-600 and the effects of the two drugs were compared.

Intracellular and extracellular potentials from both ischemic and normal myocardium were recorded with standard techniques. The tissues were stimulated by means of rectangular current pulses of variable frequency, duration and amplitude (up to 30 mA) delivered from pulse generators triggered by ramp generators through a stimulus isolation unit (Tektronix series 2600). Extrastimuli with variable amplitudes and duration could be inserted every tenth cycle. The stimulating current was calculated from the voltage, measured with a differential amplifier, across a known resistance (100 Ω) in series with one of the stimulating electrodes. The upstroke of action potentials was differentiated with a resistance-capacitance circuit or operational amplifier that was linear as high as 1000 V/sec. The durations of action potentials were measured to 100% repolarization. Conduction was assessed by measuring conduction times and distances between sites of recording and stimulation.

Because of the presence of postrepolarization refractoriness in ischemic cells, refractoriness in the IZ was defined in terms of changes of the character of the action potential generated at varying coupling intervals. During a basic driving rate associated with regular repetition of the same action potential, i.e., 1:1 response, premature stimuli were introduced every tenth paced beat at gradually shorter coupling intervals. The largest coupling interval that would result in further depression of the upstroke velocity of the premature response compared with the basic driven responses was defined as the relative refractory period. Changes in this interval after drug administration would reflect the effect of the drug on refractoriness in the IZ.

Results

In Vivo Experiments

In all experiments, verapamil and D-600 in a 0.5 mg/kg intravenous bolus injection caused slowing of the spontaneous sinus rate and an increase of AV nodal conduction delay. The latter was evidenced by lengthening of AV nodal conduction time (AH interval) as well as a decrease in the critical atrial rate that resulted in Wenckebach-type or 2:1 AV nodal block. Conduction disorders in the IZ were consistently tachycardia-dependent, with conduction markedly
dependent on changes in the cardiac cycle length. Both verapamil and D-600 improved tachycardia-dependent conduction delays in the IZ (figs. 1 and 2). In figure 1, traces from top to bottom represent standard lead 2, electrode catheter recording of the His bundle electrogram (Hbeg) and composite electrode recordings from the infarction zone (IZeg) and adjacent normal zone (NZeg). Panel A illustrates a control recording during spontaneous atrial rhythm at a cycle length of 410 msec. The NZeg was a sharp multiphasic deflection with a duration approximately equal to the QRS duration in the surface lead. On the other hand, the IZeg consisted of a multiphasic deflection, the later part of which was inscribed during the ST-T segment. This part reflected delayed activation in the IZ and is referred to in this study as the IZ potential. Exact repetition of the same configuration of the IZ potential in consecutive beats represents a 1:1 conduction pattern in the IZ.

Panels B and C illustrate the tachycardia-dependent conduction disorders in the IZ and related reentrant ventricular arrhythmias. Panel B was recorded during atrial pacing at a cycle length of 390 msec and illustrates a Wenckebach-like conduction pattern of the IZ potential and the occurrence of reentrant beats with extrasystolic grouping. Analysis of the IZeg shows that the manifest trigeminal rhythm in panel B was related to a 3:2 Wenckebach-like conduction pattern of the IZ potential. The opening beat of the Wenckebach cycle was associated with a relatively more synchronized and sharp IZ potential. During the second beat of a 3:2 Wenckebach-like cycle, the IZ potential was replaced by a continuous series of multiple asynchronous spikes that bridged the entire diastolic interval between the atrial and reentrant ventricular beats. Panel C shows that further shortening of the cardiac cycle to 360 msec resulted in a 2:1 conduction pattern of the IZ potential and disappearance of manifest reentry.

Figures 1D–F were obtained 2 minutes after intravenous bolus injection of 0.5 mg/kg of verapamil. Panel D shows slight slowing of the spontaneous atrial rhythm and significant lengthening of the AH interval from a control value of 80 msec in panel A to 125 msec. There was marked improvement in the fractionation and delay of the IZeg. Panel E was recorded during atrial pacing at a cycle length of 390 msec. Compared with the control recording at the same cycle length in panel B, there was marked improvement of the IZeg, which maintained a 1:1 conduction pattern. Concomitant with the improvement of conduction delays in the IZ, the reentrant trigeminal rhythm (panel B) had disappeared. Panel F illustrates the occurrence of AV nodal Wenckebach conduction on further shortening of the atrial cycle length to 345 msec.

Figure 2 was obtained soon after recordings in figure 1 and illustrates His bundle pacing at different

![Figure 1](http://circ.ahajournals.org/)

**Figure 1.** Recordings from a canine experiment showing that the antiarrhythmic effect of verapamil is secondary to improvement of tachycardia-dependent conduction delay in the infarction zone (IZ). See text for details. Panels A–C show control recordings. Panels D–F were obtained 2 minutes after an i.v. bolus of 0.5 mg/kg of verapamil. In this and subsequent figures, Hbeg = His bundle electrogram; IZeg = infarction zone composite electrogram; NZeg = normal zone composite electrogram; H = His bundle potential. Time lines are set at 1-second intervals.
Wenckebach-like conduction cycle lengths. Panels A and B show that a 1:1 conduction pattern of the IZ potential with limited fractionation and delay could be maintained up to a cycle length of 340 msec. However, shortening of the cycle length to 305 msec in panel C resulted in a 3:2 Wenckebach-like conduction pattern of the IZ potential and the reappearance of a reentrant trigeminal rhythm. Further shortening of the cycle length to 285 msec in panel D resulted in 2:1 conduction pattern of the IZ potential and the disappearance of manifest reentry.

Figure 3 illustrates the effect of verapamil and D-600 on conduction of the IZ potential in 17 experiments. Both verapamil and D-600 resulted in shift of the cardiac cycle length at which Wenckebach-like conduction of the IZ potential occurred to relatively short cycle lengths. The difference was statistically significant for both verapamil (p < 0.001) and D-600 (p < 0.001). There was, however, no significant change in the width of the zone associated with the Wenckebach-like conduction pattern (p > 0.2). This reflects consistent improvement of conduction in the IZ. After verapamil or D-600, the improvement of impulse conduction in the reentrant pathway could result in disappearance of manifest reentrant rhythms when the cardiac cycle length was kept constant (compare control recording in fig. 1, panel B, and the recording in fig. 1, panel E). However, because conduction delays are tachycardia-dependent in the IZ, manifest reentrant rhythms could still be induced after verapamil or D-600 injections at relatively short cardiac cycle lengths (compare fig. 1, panel B and fig. 2, panel C).

Figure 4 illustrates the effect of pretreatment with propranolol on verapamil-induced improvement of conduction in the IZ in six experiments. A smaller dose of verapamil (0.2 mg/kg) was used. Propranolol in a dose of 0.5 mg/kg that blocked the cardiac effects of isoprenaline (0.1 µg/kg) had no significant effect on the range of cardiac cycle lengths at which Wenckebach-like conduction of the IZ potential occurred (p > 0.2). Subsequent injection of verapamil (0.2 mg/kg) still resulted in a shift of the cardiac cycle length at which Wenckebach-like conduction of the IZ potential occurred to relatively short cycle lengths. The difference was statistically significant (p < 0.001). Thus, pretreatment with a β-adrenoreceptor blocking drug failed to prevent verapamil-induced improvement of conduction in the IZ.

**Effect of Verapamil on Reentrant Ventricular Arrhythmias Induced by Premature Stimulation**

Figure 5 shows control recordings from a different experiment. His bundle pacing was regularly maintained at a constant cycle length of 450 msec and His bundle premature depolarizations were introduced every fifth paced beat at gradually shorter coupling intervals. Two composite recordings from the IZ are illustrated (IZeg-1 and IZeg-2). Panel A shows that a
premature depolarization with a coupling interval of 300 msec resulted in more fractionation and delay of the IZ potential compared with the regular paced beat at a cycle length of 450 msec. Shortening of the coupling interval to 280 msec in panel B resulted in further fractionation and delay of the IZ potential. At a critical coupling interval of 260 msec in panel C, the fractionated and delayed IZ potential extended beyond the T wave of the surface ECG and resulted in a manifest reentrant ventricular tachycardia. Coupling intervals of 180–260 msec resulted in manifest reentry (panels D–F). Coupling intervals shorter than 180 msec blocked in the His-Purkinje system and did not excite the ventricular myocardium.

Figure 6 was obtained 2 minutes after an intravenous bolus injection of 0.5 mg/kg of verapamil. After verapamil injection, coupling intervals of 260–300 msec did not result in any noticeable change in the configuration and duration of the IZeg compared to regular paced beats (panels A–C). On the other hand, coupling intervals of 180–240 msec resulted in a limited degree of fractionation and delay of the IZ potential that did not extend beyond the T wave of the surface ECG (panels D–G). Consequently, these premature depolarizations failed to induce manifest reentrant rhythms. A coupling interval of 160 msec blocked in the His-Purkinje system (panel H). Figures 5 and 6 suggest that the antiarrhythmic effect of verapamil on reentrant ventricular arrhythmias initiated by premature depolarizations is most probably related to shortening of refractoriness in ischemic myocardium, resulting in improvement of conduction of premature depolarizations.

**In Vitro Experiments**

**Action Potential Characteristics in the IZ**

Cells in the IZ showed variable degrees of partial depolarization (resting potentials from −85 to −50 mV), reduced action potential amplitude and decreased upstroke velocity. The slow upstrokes were sometimes fractionated into one or more segments of negative slope or showed low-amplitude, slow-step potentials. The inhomogeneity of action potentials was apparent by the finding of relatively good intracellular responses in cells only a few millimeters from other cells that were practically unresponsive. Conduction in the IZ was heterogeneously slowed to values less than 0.01 mm/sec, resulting in irregular wave fronts. Values for conduction velocity were only approximate because of the inherent difficulty in evaluating conduction velocity in a syncytial structure like the myocardium as well as the inhomogeneity of tissues encompassed between the recording and stimulating electrodes. Further evidence of inhomogeneity was the presence of widely disparate refractory periods in cells in close proximity to one another.

Full recovery of responsiveness frequently outlasted the action potential duration reflecting the presence of postrepolarization refractoriness. In these cells,
Figure 5. Control recordings from a different experiment showing ventricular reentry initiated by premature depolarizations. Regular His bundle pacing was applied at a constant cycle length of 450 msec and His bundle premature depolarizations were introduced every fifth paced beat at gradually shorter coupling intervals. See text for details.

Figure 6. Recordings were obtained from the same experiment shown in figure 5, 2 minutes after an i.v. bolus of 0.5 mg/kg verapamil. These recordings illustrate that the antiarrhythmic effect of verapamil on ventricular reentry initiated by premature depolarizations resulted from improved conduction in the ischemic zone (IZ). Eg = electrogram.
premature stimuli would elicit graded responses over a wide range of coupling intervals. Critically coupled premature stimuli could frequently result in one or more spontaneous beats. Conduction in myocardial cells was invariably greatly slowed and irregular when abnormal spontaneous beats occurred, suggesting that the mechanism of the spontaneous beats was reentry involving depressed ischemic cells. However, there was no evidence of abnormal automaticity in the ischemic zone. In some cells, full recovery of responsiveness was not complete up to 1000–2000 msec. For these cells, regular pacing at relatively short cycles would result either in a 2:1 response or a Wenckebach-like pattern of conduction block. A Wenckebach-like conduction pattern could be commonly elicited in ischemic cells. This is illustrated in figure 7. Intracellular recordings were obtained from two myocardial cells 5 mm apart in the infarction zone. The two cells had widely different resting potentials. The cell at site Y was only slightly depolarized (resting potential of −80 mV), but it still showed a poor action potential. This observation suggests that responses of ischemic cells might be depressed by factors other than the decrease of resting potential. Pac- ing at a cycle length of 290 msec resulted in a synchronous Wenckebach-like conduction pattern at the sites of both intracellular recordings and the extracellular electrogram. The action potentials of the opening beat of the Wenckebach-like cycle showed a relatively rapid but still abnormally slow upstroke. The second and third beats of the cycle showed a slow initial step followed by a more rapid but still abnor- mally slow upstroke. In the last beat of the Wenckebach cycle (illustrated at the beginning of the record), the rapid upstroke failed to be inscribed and only a long slow step was recorded.

The extracellular bipolar electrogram (marked by arrows) coincided with the relatively rapid upstrokes and illustrated the occurrence of gradual conduction delay before failure of conduction during the last beat of the Wenckebach-like cycle. In figure 7, the pacing cycle length that resulted in a Wenckebach-like conduction pattern exceeded the action potential duration of the two cells in the IZ, suggesting that full recovery of responsiveness extended beyond the action potential duration, reflecting the presence of postrepolarization refractoriness.

Effect of D-600 and Tetrodotoxin on Ischemic Myocardial Cells

Figure 8 contrasts the effect of tetrodotoxin and D-600 on ischemic myocardial cells in the same preparation. The control recording shows an ischemic (X) and normal (Y) myocardial cell and two close bipolar electrograms from normal (1) and ischemic (2) zones. The resting potential of the ischemic cell was only slightly lower than the normal cell. However, the ischemic cell had a reduced action potential amplitude and a decreased upstroke velocity. The normal zone electrogram showed a sharp biphasic deflection, while the ischemic zone electrogram was fractionated with low amplitude and a slow deflection. Tetrodotoxin results in slight reduction of the upstroke velocity of the normal cell and slight widening of the normal zone electrogram. There was no change in the resting potential. Tetrodotoxin greatly attenuated the action potential

![Figure 7](image-url)

**Figure 7.** Recordings from an in vitro experiment illustrating action potential characteristics in ischemic epicardium. The sketch of the preparation shows two intracellular recordings (X and Y) and a close bipolar recording (1) from the infarction zone (the hatched area). Ischemic cells had decreased upstroke velocity, reduced action potential amplitude, and a variable degree of partial depolarization. The two cells were recorded 5 mm apart in the infarction zone, but showed significant difference in their resting potential. The resting potential of the Y cell was only slightly reduced (−80 mV), but it still had a poor action potential. The preparation was stimulated at a cycle length of 290 msec that resulted in a Wenckebach-like conduction pattern. Note that the pacing cycle length exceeded the action potential duration of the two cells, suggesting that refractoriness extended beyond the completion of the action potential, i.e., postrepolarization refractoriness.
of the ischemic cell and abolished the ischemic zone electrogram, illustrating the marked sensitivity of ischemic cells to the depressant effect of tetrodotoxin. The more depressed ischemic cells were highly sensitive to the drug, and their action potentials were either abolished or greatly attenuated on exposure to tetrodotoxin. The third panel in figure 8 illustrates the return to control recording after washing tetrodotoxin. The effect of subsequent exposure to D-600 is shown in the last panel. D-600 had no effect on the resting potential or action potential amplitude of the normal cell and caused an insignificant shortening of the action potential duration. However, in marked contrast to the effect of tetrodotoxin, D-600 resulted in slight improvement of the upstroke velocity of the ischemic cell and a noticeable improvement of conduction of the ischemic zone electrogram.

In other experiments, D-600 also resulted in improved recovery of responsiveness of ischemic cells with shortening of postrepolarization refractoriness. This allowed premature stimuli to elicit better responses with less depressed upstroke velocities and improved conduction.

**Discussion**

**Refractoriness in Ischemic Myocardium**

Recent studies of electrophysiologic changes of myocardial cells in the first few minutes after ligation of a coronary artery show that the refractory period begins to lengthen while action potential duration continues to shorten.\(^1\) Such discrepancy between action potential duration and recovery of excitability was originally described in isolated fibers of ischemic His-Purkinje system and was called postrepolarization refractoriness.\(^4,\)\(^5\) Postrepolarization refractoriness was also a prominent feature of the ischemic myocardium in the late myocardial infarction period.

Our observation that grossly disparate recovery times could coexist in cells in close proximity in the ischemic zone is similar to observations in the acutely ischemic myocardium.\(^3\) As a result, the conventional test stimulus method of refractory period measurement in vivo has serious limitations when applied to ischemic myocardium, since it is expected to reflect only the shortest recovery time in the vicinity of the stimulation site.\(^3\) More accurate evaluation of changes of refractoriness in the infarction zone could probably be obtained by analysis of changes in the configuration and duration of the composite electrogram in response to varying coupling intervals as was applied in the present study. However, since the composite electrogram averages the recordings from multiple close bipolar points, it may sometimes be difficult to discern the loss (i.e., block) of the electrical signal of part of the ischemic zone.

**Ionic Conductance Abnormalities in Ischemic Myocardium**

The slow-response action potentials were implicated in the genesis of reentrant arrhythmias because of their propensity for very slow propagation with a low safety factor for conduction.\(^3,\)\(^6,\)\(^7\) Slow-response action potentials could be artificially produced by

![Figure 8](http://circ.ahajournals.org/figure/8)
depolarizing normal Purkinje fibers by high extracellular potassium (K⁺) to levels of membrane potential where the rapid Na⁺ channel would be inactivated, and by enhancing the slow channel by adding catecholamine.¹⁷⁻²⁰ This model of slow-response action potentials satisfied the requisite for the occurrence of reentrant ventricular arrhythmias.¹¹, ²¹ The contrived slow-response action potential was also readily depressed by verapamil and D-600.²⁰

The analogy has been drawn between the K⁺ depolarized catecholamine-stimulated Purkinje fiber model for slow response action potentials and ionic conductance abnormalities in acute ischemia.²² It has been postulated that in the ischemic zone, high concentrations of extracellular K⁺ may depolarize the cells to the extent that the rapid Na⁺ channel is inactivated and high concentrations of catecholamines may stimulate the slow channel, resulting in slow-response action potentials. The latter would explain slowed conduction and reentrant ventricular arrhythmias associated with ischemia. Although a high K⁺, high-catecholamine environment is plausible in the early stages of ischemia,²³⁻²⁴ the postulate is weakened by several considerations. The principal role of high extracellular K⁺ in electrophysiologic abnormalities of acute ischemia was questioned in a recent study by Downinger et al.²⁵ Furthermore, the effects of verapamil on conduction delays in ischemic myocardium during the early stages of ischemia are controversial.²⁶, ²⁷ The K⁺-depolarized, catecholamine-stimulated Purkinje fiber model and the slow-response action potential concept loses much of its plausibility in the later stage of myocardial infarction, as in the case of the present model. The extracellular K⁺ concentration at this stage is not exactly known, but is probably not as high as in the early stage of ischemia. Besides, total catecholamines decline in the ischemic region to a very low level on the day after coronary occlusion.²⁸ However, ischemic myocardium still shows markedly depressed action potentials, slow conduction, and a high propensity for reentrant rhythms.

Depressed ischemic cells were exquisitely sensitive to the depressant effect of tetrodotoxin, a specific blocker of the fast Na⁺ channel.⁶, ²⁸ Contrary to what would be expected from the effect of verapamil and D-600 on a slow-response action potential, these two drugs did not depress, but rather improved poor membrane responses of ischemic myocardial cells. Theoretically, the effect of D-600 in the present study may be explained by suggesting that ischemia results in a host of responses, including depressed fast responses and slow responses, and that D-600 would abolish the latter responses. Because of electrotonic interaction, this effect of D-600 could result in improved upstroke velocity of depressed fast responses. These assumptions are, however, refuted because we could not demonstrate slow responses that were further depressed or abolished by D-600. On the contrary, our observations strongly suggest that the slow inward current does not play a role in the transmission of the cardiac impulse in ischemic myocardium, at least in the late myocardial infarction period. Also significant is our failure to demonstrate spontaneous or triggered abnormal automaticity in ischemic myocardium at this stage. Poor membrane responses of ischemic myocardial cells appear to be related to depression of the fast Na⁺ channel. Unlike Purkinje fibers, myocardial cells may be particularly susceptible to partial depression of the fast channel with further impairment of recovery from inactivation of the Na⁺ current.²⁹ The latter would explain the marked prolongation of postrepolarization refractoriness of ischemic myocardial cells observed in this study.

Mechanisms of the Antiarrhythmic Effect of Verapamil and D-600 on Reentrant Ventricular Arrhythmias

This study has clearly demonstrated that both verapamil and D-600 owe their antiarrhythmic effect on reentrant ventricular arrhythmias in the late myocardial infarction period to improved conduction in the reentrant pathways. Improvement of depressed membrane responses of ischemic myocardial cells by verapamil and D-600 may be related to either hemodynamic and metabolic effects of the drugs³⁰, ³¹ or to a direct electrophysiologic action. Verapamil has been shown to reduce the extent of ischemic injury after coronary artery ligation.³² However, it probably will not have a similar effect when administered 3–7 days after myocardial infarction, as in the present study. Verapamil in a dose of 0.1 mg/kg or less was found to cause peripheral vasodilatation, which leads to reflex increase of the sympathetic tone.³³ A recent study has shown that verapamil-induced catecholamine release may enhance electrophysiologic properties of depressed Purkinje fibers.³⁴ Both the in vivo and in vitro observations in this study have shown that verapamil and D-600 improve depressed responses of ischemic myocardial cells in doses of 0.5 mg/kg in vivo and 0.5–1 mg/l in vitro. These doses were not associated with reflex catecholamine release.³² Furthermore, pretreatment with propranolol did not prevent the enhancing effect of a smaller dose of verapamil in vivo (0.2 mg/kg). In a separate study, we have shown that marked stimulation of the cardiac sympathetic nerves resulted in only slight enhancing effect on conduction in the ischemic zone.³⁴ The possibility that verapamil and D-600 would increase myocardial blood flow to the epicardial ischemic zone and that this effect would improve membrane responses of ischemic myocardial cells has not been investigated in this study but seems unlikely to be a major contributing factor.

Our in vitro observations clearly illustrate that at least part of the D-600-induced improvement of depressed ischemic cells is due to a direct electrophysiologic action on altered membrane responses. In a recent in vitro study, verapamil was found to shorten action potential duration of K⁺-depolarized ventricular fibers, but had no effect on Vmax kinetics.³⁶ Shortening of the action potential duration indirectly resulted in an increased upstroke velocity of early premature action potentials. In the present study,
however, D-600 was found to improve the upstroke velocity of nonpremature action potentials. Improved responses of premature action potentials was related to shortening of postpolarization refractoriness rather than to shortening of action potential duration. The exact mechanism by which verapamil or D-600 would improve the kinetics of ischemia-induced depressed fast channel as well as the abnormally delayed recovery of inactivation of the Na+ current is largely unknown. Some studies have shown the action of D-600 to be complex, involving not only reduction of the maximal Ca++ conductance, but also a change in both the kinetics of the Ca++-carrying system and the amplitude of the steady state outward current.36 Perhaps verapamil or D-600 may improve the depressed Na+ channel by a sparing effect on endogenous energy resources. This possibility is, however, perturbed by incomplete understanding of the energy requirement of both normal and depressed Na+ channel.37

Conclusions

Studies on the mechanism of action of antiarrhythmic drugs have suffered from at least two basic flaws. First, data obtained from studies in normal cardiac cells were applied, sometimes indiscriminately to the pathologic situation. Second, information gained from artificial models of arrhythmias have sometimes led to incorrect assumptions. It is generally assumed that the two mechanisms by which an antiarrhythmic agent can exert its effect on reentrant rhythms are either further depression and block of the reentrant pathway or improvement of conduction in the pathway.38 Ironically, the two drugs that were presumed to act by improving conduction in reentrant pathways (lidocaine and diphenylhydantoin) were later shown to owe their antiarrhythmic effect to selective depression of conduction of poor response action potentials forming part of the reentrant pathway.4-6, 39-41

On the other hand, the two drugs that were suggested to abolish reentrant ventricular rhythms by depression of conduction in the reentrant pathway (verapamil and D-600) were shown in this study to exert their antiarrhythmic effect by improving conduction in the pathway. The effect of verapamil and D-600 on ischemia-related reentrant ventricular arrhythmias raises the question of whether it is desirable or practical for an ideal antiarrhythmic drug to act by selectively depressing or by improving conduction of depressed cells forming part of the reentrant pathway. In this regard, our observations suggest that verapamil is probably a weaker antiarrhythmic drug compared with lidocaine in reentrant ventricular arrhythmias in the late myocardial infarction period. This may suggest that an ideal antiarrhythmic drug in ischemia-related reentrant ventricular arrhythmias should probably selectively depress rather than improve membrane responses of depressed cells critically involved in the establishment of successful reentrant circuits.

Our observations suggest that the mechanisms of action of lidocaine and verapamil on ischemic myocardial cells are more or less diametrically opposite, with lidocaine further depressing abnormal fast response action potentials while verapamil slightly improves the depressed Na+ channel. It would be expected that the administration of both drugs in rapid succession in the same case may nullify each other's effects. Our preliminary observations using the present canine model shows this to be largely correct. This observation is another argument in favor of a more rational approach to the largely empirical practice of antiarrhythmic therapy.

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