Re-entrant Ventricular Arrhythmias in the Late Myocardial Infarction Period

5. Mechanism of Action of Diphenylhydantoin

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SUMMARY The mechanism of action of diphenylhydantoin (DPH) on re-entrant ventricular arrhythmias (RVA) was studied in dogs 3–7 days following ligation of the anterior descending coronary artery utilizing direct recordings of the re-entrant pathway (RP) from the epicardial surface of the infarction zone (IZ). DPH in a therapeutic dose consistently prolonged refractoriness of potentially RP in the IZ. This resulted in further impairment and/or block of conduction in the RP and was directly responsible for DPH ability to abolish RVA. On the other hand, DPH had no significant effect on conduction in the adjacent normal zone. Prior to abolition of RVA initiated by premature beats (PBs), DPH resulted in: 1) narrowing of the critical range of coupling intervals of PBs that resulted in re-entry (i.e., the re-entry zone), 2) shift of the narrowed re-entry zone to longer cardiac cycle lengths, and 3) lengthening of the coupling interval of the first re-entrant beat, as well as slowing the rate of re-entrant tachycardia. Thus DPH, similar to lidocaine, owes its antiarrhythmic action in RVA to its selective depressant effect on ischemic cells forming part of the RP.

Since initial experimental reports by Harris and Kokernot¹ and Mosey and Tyler² of diphenylhydantoin (DPH) has been shown to be an effective agent in abolishing various experimental and clinical cardiac arrhythmias in a variety of situations including digitalis toxicity and acute myocardial infarction.³–⁴ However, the mechanism of the antiarrhythmic action of DPH has given rise to considerable controversy. Most investigators agree that the drug depresses spontaneous diastolic depolarization and is effective in arrhythmias due to enhanced automaticity.⁵,⁶,⁷ The controversy centers on the effects of DPH on electrophysiologic parameters such as membrane responsiveness and conduction velocity in cardiac cells, which can be major determinants in the establishment or abolition of re-entrant arrhythmias. Bigger et al.⁸ and Strauss et al.⁹ found that DPH in therapeutic concentrations did not decrease membrane responsiveness or conduction velocity. On the contrary, it actually increased these two parameters in addition to abbreviation of both the action potential duration and effective refractory period especially in depressed cardiac cells. The efficacy of DPH in abolishing re-entrant rhythms was thus attributed to improvement of conduction in the re-entrant pathway.¹⁰,¹¹,¹² On the other hand, other investigators have found that DPH effects on cardiac cells are not dissimilar to those of quinidine,¹³ producing marked retardation of conduction velocity and depression of membrane responsiveness particularly in the presence of higher extracellular levels of potassium.¹⁴,¹⁵ These findings would suggest that DPH, similar to quinidine, may interrupt re-entrant cycles by conversion of a one-way block into a two-way block.¹⁶

We have recently analyzed the mechanism of action of lidocaine in re-entrant ventricular arrhythmias in dogs 3–7 days post myocardial infarction¹⁷ using a remarkably stable canine model in which direct recordings of the elec-
trical activity of the re-entrant pathway(s) were obtained.\textsuperscript{25–27} Lidocaine in a therapeutic dose was found to “selectively” prolong refractoriness and depress conduction in re-entrant pathways in ischemic myocardium while having no effect on conduction in adjacent normal zone.\textsuperscript{24} Depression and/or block of conduction in the re-entrant pathway was the mechanism by which lidocaine abolished re-entrant ventricular arrhythmias. The electrophysiologic effects of lidocaine were reported to be remarkably similar to DPH.\textsuperscript{15, 18, 19} Further, prior to our recent study, the main controversial arguments relating to the mechanism of action of DPH in re-entrant arrhythmias equally applied to lidocaine.\textsuperscript{15, 18, 19, 22, 24} Therefore, this study was conducted to test the theory that DPH, similar to lidocaine, acts by selective depression of conduction in the re-entrant pathway.

**Material and Methods**

The results included in this study were obtained from 15 adult mongrel dogs that were studied 3–7 days following ligation of the left anterior descending artery just distal to the anterior septal branch. All dogs showed evidence of infarction involving the subepicardial layer of muscle. Recordings were obtained from the epicardial surface of the infarction zone (IZ) and adjacent normal zone (NZ). A specially designed composite electrode that depicts an averaged recording of multiple close bipolar sites was utilized. In addition, 1–3 close bipolar recordings were also obtained. Details of the surgical procedure and the recording techniques were described elsewhere.\textsuperscript{26} In addition to the electrograms, two standard electrocardiographic (ECG) leads were recorded, specifically leads II and aVR. All records were obtained on a multichannel oscilloscopic photographic recorder (E for M, DR-8) at paper speeds of 25–200 mm/sec. Electrocardiograms were recorded with the preamplifier set for frequencies of 0.1–200 cycles/sec and bipolar electrograms were recorded with filter frequencies of either 40–200 cycles/sec or 12–200 cycles/sec. Measurements were accurate within ±3 msec at a paper speed of 200 mm/sec.

In all experiments, the sinus node area was either crushed or excised through a separate right thoracotomy incision. Recordings were then obtained during atrial or His bundle pacing as well as programmed premature stimulation. Details of the pacing procedures were described elsewhere.\textsuperscript{25, 26}

Diphenylhydantoin (10 mg/kg) was injected intravenously over a three minute period and the effects on conduction in IZ as well as on re-entrant ventricular arrhythmias were continuously monitored in the ECG leads and in the IZ and NZ electrograms for at least 30 min after the injection. In some experiments, the effects of a smaller dose of DPH (5 mg/kg) were initially tested. Forty-five minutes were allowed for return to control, then the effects of the large dose of 10 mg/kg were compared in the same experiment.

**Results**

**Effect of DPH on Conduction in the Infarction Zone**

Our previous observations have shown that conduction disorders in the IZ were consistently tachycardia-dependent with the conduction being markedly dependent on changes in the cardiac cycle length.\textsuperscript{25–27} DPH resulted in characteristic changes in the rate-related conduction disorders in the IZ. This is shown in figure 1. Traces from top to bottom represent standard lead 2, an 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 atrial pacing at a cycle length of 500 msec. The NZeg was a 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 fractionated deflection, the later part of which was inscribed in the diastolic period during the ST-T segment. As was explained elsewhere,\textsuperscript{25} this part reflected delayed activation in the IZ and is referred to in this study as the IZ potential (marked by an arrow). Exact repetition of the same configuration of the IZ potential in consecutive beats is taken to represent a 1:1 conduction pattern in the IZ. In all experiments, there was a critical narrow range of relatively short cardiac cycle lengths, that varied from one experiment to the other, during which the conduction pattern changed to a Wenckebach-like arrangement with periodic changes in the IZ potential.\textsuperscript{25} Further decrease of the cycle length would result in a 2:1 block of part or all of the IZ potential. This is illustrated in panels B to D which were obtained during His bundle pacing applied through the electrode catheter recording the His bundle potential. During these recordings the His bundle electrogram was replaced by an atrial electrogram (RAeg). Panel B shows that pacing at a cardiac cycle length of 370 msec was still associated with a 1:1 conduction pattern of the IZ potential. Panel C shows the occurrence of a regular 3:2 Wenckebach-like conduction pattern of the IZ potential. The opening beat of the Wenckebach cycle was associated with a relatively narrow and more synchronized IZ potential (marked by an arrow). During the second beat of a 3:2 Wenckebach-like cycle, the IZ potential was fractionated into a continuous series of asynchronous deflections ending with a relatively sharp spike (marked by an arrow) that extended late in the diastolic interval. The third beat of the 3:2 Wenckebach-like cycle showed failure of inscription of a major part of the IZ potential. Panel D shows that further shortening of the cardiac cycle length to 285 msec resulted in a 2:1 block of the IZ potential.

Panels E to G in figure 1 were obtained following intravenous injection of 10 mg/kg of DPH. Panel E shows that a cycle length of 500 msec was associated with slight widening of the IZ potential compared to control recording in panel A but a 1:1 conduction pattern was still maintained. Shortening the cardiac cycle length to 370 msec in panel F resulted in the occurrence of a 3:2 Wenckebach-like cycle of the IZ potential. The same cycle length was associated with a 1:1 conduction pattern of the IZ potential during control recording in panel B. Compared to the control recording in panel C there was more fractionation of the IZ potential during the second beat of the 3:2 Wenckebach-like cycle as well as failure of inscription of the relatively sharp late spike shown in panel C. Panel G shows the occurrence of a 2:1 conduction block of the IZ potential on a slight further shortening of the cardiac cycle length to 365 msec.
Analysis of figure 1 shows that DPH resulted in lengthening of refractoriness in areas of the IZ represented by the IZ potential. This would explain the occurrence of rate-related higher degree of conduction block (Wenckebach-like conduction periodicity and 2:1 block of the IZ potential) at relatively long cardiac cycle lengths. However, the conduction disorder induced by DPH was still tachycardia-dependent since conduction improved at relatively slow heart rates. On the other hand, analysis of figure 1 shows that DPH had no effect on the NZeg or the QRS configuration and duration in the surface lead. This emphasizes the selective depressant effect of DPH on conduction in the IZ.

Figure 2 summarizes the effects of DPH on conduction of the IZ potential in 10 different experiments. The figure shows that following DPH the critical range of cardiac cycle lengths associated with Wenckebach-like conduction pattern of the IZ potential consistently became relatively long but without significant change in the width of the zone associated with the Wenckebach-like conduction pattern. The figure also illustrates that the smaller dose of DPH (5 mg/kg) consistently resulted in worsening of the rate-related conduction disorders of the IZ potential. However, the effects of the smaller dose were always less marked than those of the larger dose (10 mg/kg) in the same experiment. This emphasizes the dose-related depressant effect of DPH on conduction in the IZ.
Effect of DPH on Re-entrant Ventricular Arrhythmias

Figures 3-5 were obtained from the same experiment shown in figure 1 and illustrate the effect of DPH on re-entrant ventricular rhythms initiated by premature beats. Figure 3 shows control recordings. His bundle pacing was regularly maintained at a constant cycle length of 500 msec and His bundle premature beats were introduced every fifth paced beat at gradually shorter coupling intervals. Panel A shows that a premature beat with a coupling interval of 320 msec resulted in more fractionation and delay of the IZ potential compared to the regular paced beat at a cycle length of 500 msec. Further shortening of the coupling interval to 300 msec in panel B resulted in further fractionation and delay of the IZ potential. At a critical coupling interval of 295 msec in panel C, the fractionated and delayed IZ potential resulted in a manifest re-entrant beat. Premature beats with coupling intervals between 245 and 295 msec resulted in manifest re-entry (panel D). Panel E shows that further shortening of the coupling interval of the premature beat to 240 msec resulted in loss of inscription of the IZ potential denoting conduction block in the re-entrant pathway. Further shortening of the coupling interval in panel F was still associated with conduction block in the re-entrant pathway and no re-entry. The short coupling, however, resulted in aberrant intraventricular conduction of the premature beat. The figure illustrates that the critical range of coupling intervals of premature beats that initiated a manifest re-entrant rhythm (i.e., the re-entry zone) was 50 msec. During manifest re-entry, the coupling interval of the first re-entrant beat which reflects the re-entrant pathway conduction time was 250–285 msec.

Figure 4 was obtained immediately following the injection of 10 mg/kg of DPH. Compared to control recordings in figure 3, DPH resulted in the following significant changes: 1) Premature beats with relatively long coupling interval (340 and 330 msec in panels B and C, respectively) produced marked fractionation and delay of the IZ potential resulting in manifest re-entry. The amplitude of the fractionated IZ potential associated with re-entry was significantly lower compared to control recordings in figure 3, panels C and D. 2) The range of coupling intervals of premature beats that resulted in re-entry (the re-entry zone) was markedly abbreviated compared to control (10 msec compared to 50 msec in fig. 3). Panel D shows that although a premature beat with a coupling interval of 320 msec was still associated with some fractionation of the IZ potential it did not result in manifest re-entry. In panel E, a premature beat with a coupling interval of 300 msec resulted in loss of inscription of a major part of the IZ potential reflecting the occurrence of conduction block at a proximal site in the re-entrant pathway. Further shortening of the coupling interval in panels F and G was still associated with conduction block in the re-entrant pathway and no re-entry. 3) The coupling interval

Figure 3. Recordings obtained from the same experiment shown in figure 1 that illustrate ventricular re-entry initiated by premature beats. Regular His bundle pacing was applied at a constant cycle length of 500 msec and His bundle premature beats were introduced every fifth paced beat at gradually shorter coupling intervals. The figure shows that premature beats with coupling intervals between 245 and 295 msec resulted in manifest re-entry (a re-entry zone of 50 msec). (panels C and D). During re-entry the IZ potential fractionated into a continuous series of asynchronous spikes that bridged the entire diastolic interval between the premature paced beat and the re-entrant beat. Premature beats with coupling intervals longer than 295 msec (panels A and B) and shorter than 245 msec (panels E and F) resulted, respectively, in a lesser degree of fractionation and delay of the IZ potential and block of the potential and were not associated with manifest re-entry.
of the first re-entrant beat that reflects the re-entrant pathway conduction time was significantly prolonged compared to the control (from 250–285 msec before DPH to 350–380 msec following DPH).

Figure 5 was obtained 2 min following the recordings in figure 4. It illustrates complete failure of premature beats to initiate manifest re-entry reflecting complete obliteration of the re-entry zone. Although premature beats with coupling intervals of 335–390 (panels A–D) still resulted in varying degrees of fractionation and delay of the IZ potential they failed to result in manifest re-entry. This probably reflects conduction block at different levels in the re-entrant pathway. On the other hand, premature beats with coupling interval of 320 msec or shorter were associated with loss of
inscription of a major part of the IZ potential reflecting conduction block at a more proximal site in the re-entrant pathway (panels E–H).

Analysis of figures 3–5 shows that DPH has no significant effect on conduction in the NZ or the QRS duration and configuration in the surface lead. Comparison of the QRS configuration of the premature beat with the short coupling interval of 220 msec in figures 3–5 emphasizes this observation by showing no significant change in the degree of aberrant intraventricular conduction following DPH injection.

The effects of DPH on re-entry initiated by premature beats in 10 different experiments are summarized in table 1. DPH resulted in obliteration of the re-entry zone in five experiments. In three of these experiments recordings obtained immediately following the injection of the drug showed initial narrowing of the re-entry zone before obliteration (figs. 3–5). The re-entry zone was narrowed in two other experiments but was not completely obliterated, was lengthened in two and unchanged in one. In the five experiments in which narrowing of the re-entry zone was demonstrated, the coupling intervals of premature beats that still resulted in re-entry were relatively long compared to control (figs. 3 and 4). Also, the coupling intervals of the first re-entrant beat were longer following DPH compared to control. In one experiment (38) premature beats initiated a regular re-entrant ventricular tachycardia at a rate of 280/min. DPH resulted in narrowing of the re-entry zone and the rate of the re-entrant tachycardia that could still be induced after DPH was relatively slow at 210/min.

In the experiment shown in figures 3–5 only one re-entrant pathway was probably operative judging from the constant QRS configuration of manifest re-entrant beats. However, because the composite IZeg averaged the recordings from multiple sites in the IZ, slight or major variations in the re-entrant pathway cannot be excluded although the terminal part of the re-entrant pathway probably did not vary significantly. In other experiments, however, the re-entry zone encompassed several potentially re-entrant pathways as revealed by the different QRS configurations of re-entrant beats, as well as varying patterns of the fractionated IZ potential. DPH resulted in abolition of one or all of these re-entrant pathways as reflected by failure to initiate certain re-entrant beats with a particular QRS configuration. Extensive epicardial mapping could possibly have resulted in better understanding of the effect of DPH on the different potentially re-entrant pathways in the IZ.

The effect of DPH was studied in three other experiments that showed re-entrant beats with regular extrasystolic grouping (one bigeminal rhythm and two trigeminal rhythms), and in two instances of regular re-entrant ventricular tachycardia. Similar to what was described in more detail in the report on lidocaine, DPH resulted in lengthening of the coupling interval of extrasystolic beats before abolition of manifest re-entry. DPH also resulted in slowing of the rate of ventricular tachycardia before its termination.

**Discussion**

The present study clearly shows that DPH in a dose of 5–10 mg/kg, which is similar to those shown to be associated with clinical therapeutic blood levels consistently prolonged refractoriness of potentially re-entrant pathways in the IZ. This resulted in further impairment of conduction in the re-entrant pathway and was directly responsible for the ability of DPH to abolish manifest re-entrant arrhythmias. Similar to lidocaine, there was evidence that DPH gradually slowed conduction in the re-entrant pathway prior to the abolition of manifest re-entry which was characteristically associated with complete block in the re-entrant pathway. On the other hand, DPH in the dose utilized had no significant effect on refractoriness or conduction in the closely bordering NZ. Thus, both DPH and lidocaine were found to exert their antiarrhythmic action on ischemic re-entrant ventricular arrhythmias by "selectively" prolonging refractoriness of different segments of the re-entrant pathway resulting in further impairment of the already slow re-entrant wave front to the point of complete block. This action is essentially similar, though not identical, to that of quinidine. The difference lies in the greater degree of selectivity of both DPH and lidocaine which in contrast to quinidine does not depress normal cardiac cells at concentrations associated with a therapeutic antiarrhythmic action.

In the study on lidocaine we have illustrated in some detail the mechanism by which the drug abolishes manifest re-entrant beats with extrasystolic grouping as well as its action on re-entrant ventricular tachycardias. Details of DPH action on these two arrhythmias are essentially the same. On the other hand, we have demonstrated in the present study

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**Table 1. Effect of Diphenylhydantoin on Re-Entry Initiated by Premature Beats**

<table>
<thead>
<tr>
<th>Experiment no.</th>
<th>Control CI of PBs initiating reentry (msec)</th>
<th>Control CI of first RB (msec)</th>
<th>Diphenylhydantoin CI of PBs initiating reentry (msec)</th>
<th>Diphenylhydantoin CI of first RB (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>310-340</td>
<td>310-330</td>
<td>re-entry abolished</td>
<td>--</td>
</tr>
<tr>
<td>2</td>
<td>320-355</td>
<td>380-405</td>
<td>re-entry abolished</td>
<td>--</td>
</tr>
<tr>
<td>4</td>
<td>230-280</td>
<td>220-260</td>
<td>310-320–re-entry abolished</td>
<td>300-320</td>
</tr>
<tr>
<td>5</td>
<td>240-300</td>
<td>240-290</td>
<td>290-320–re-entry abolished</td>
<td>340-380</td>
</tr>
<tr>
<td>6</td>
<td>280-325</td>
<td>285-320</td>
<td>275–325</td>
<td>320-360</td>
</tr>
<tr>
<td>7</td>
<td>220-265</td>
<td>225-255</td>
<td>250-270</td>
<td>260-315</td>
</tr>
<tr>
<td>8</td>
<td>200-275</td>
<td>210-280</td>
<td>270-295</td>
<td>220-300*</td>
</tr>
<tr>
<td>9</td>
<td>250-290</td>
<td>240-260</td>
<td>230-300</td>
<td>240-340</td>
</tr>
<tr>
<td>10</td>
<td>220-270</td>
<td>210-300</td>
<td>200-290</td>
<td>260-370</td>
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</tbody>
</table>

Abbreviations: CI = coupling interval; PB = premature beat; RB = reentrant beat.

*Rate of reentrant ventricular tachycardia following DPH was 210/min compared to a control rate of 280/min.
the effect of DPH on re-entry initiated by premature beats. We found that prior to abolition of re-entry initiated by premature beats, DPH resulted in the following characteristic changes: 1) narrowing of the re-entry zone, 2) shift of the narrowed re-entry zone to longer cardiac cycle lengths, 3) lengthening of the coupling of the first re-entry beat as well as slowing the rate of re-entrant tachycardia. All three changes could be interpreted as evidence that DPH has resulted in prolongation of refractoriness of different segments of the re-entrant pathway. The abolition of re-entry which occurred shortly afterwards is explained by further prolongation of refractoriness resulting in consistent block of conduction of premature beats.

Lidocaine was found to have a more consistent effect in abolishing re-entry initiated by premature beats compared to DPH. This may be interpreted as evidence that lidocaine exerts a more effective antiarrhythmic action on ischemic re-entrant ventricular arrhythmias relative to DPH at comparable therapeutic concentrations. This may also be in line with the clinical impression about their comparative efficacy in the setting of acute or subacute myocardial infarction arrhythmias. However, comparison of the clinical efficacy of antiarrhythmic agents in general and especially those with essentially similar mechanisms of action is fraught with difficulties. This is partly related to such factors as: 1) subtle variations between one animal experiment and the other, as well as between different clinical cases; 2) differences in the dose-related responses of various drugs and the relationship between the therapeutic and toxic concentrations; 3) differences in drug sequestration by serum proteins, as well as the rate of delivery to arrhythmogenic zones in the heart; 4) modifying action of ancillary effects of the drug such as their influence on the autonomic nervous system.

Our observations on the effects of DPH and lidocaine on re-entry induced by premature beats are potentially relevant to clinical studies dealing with the efficacy, as well as the mechanism of action, of various antiarrhythmic agents on re-entrant ventricular rhythms. Analysis of the effect of an antiarrhythmic agent on conduction in a potentially re-entrant pathway can probably be more accurately assessed by such parameters as change in the critical range of cycle lengths associated with Wenckebach-like conduction of the IZ potential (figs. 1 and 2). However, this kind of information is not available in clinical studies due primarily to limitations in the recording techniques. On the other hand, clinical studies can assess the effects of antiarrhythmic agents on ventricular re-entry induced by premature beats. The findings that a drug can narrow or obliterate the re-entrant zone, shift the latter to longer cycle lengths and lengthen the coupling interval of the first re-entry beat, as well as slow the rate of re-entrant tachycardia, are evidence that the drug is effective in prolonging refractoriness of the re-entrant pathway, as well as being a potentially useful therapeutic agent in a clinical situation. Wellsens et al. have reported preliminary observations on the effect of various antiarrhythmic agents on ventricular re-entry initiated by premature beats. Their findings suggest that the effects of procainamide on the electrophysiologic properties of the re-entrant circuit in patients with re-entrant ventricular tachycardia are essentially similar to those described in this study for DPH.

In the study on lidocaine we cautioned against the possibility that a drug that owes its antiarrhythmic properties to the further impairment of the already slow conduction in a re-entrant pathway may have the potential to create successful re-entrant circuits by critically slowing conduction in moderately depressed cells. The finding in the present study that DPH lengthened the re-entry zone in two experiments may be interpreted as evidence that the drug by virtue of its depressant properties resulted in the recruitment of new potentially re-entrant pathways with or without being successful in blocking the original re-entrant circuits. However, it would be expected that the potential of both DPH and lidocaine to create new potential pathways at a therapeutic concentration is far less compared to quinidine or procainamide with their less selective depressant properties.

The results of the present study on DPH, together with the recent study on lidocaine, help to clarify in a substantial way the controversy that shrouded the mechanism of action of both drugs on re-entrant arrhythmias for a long time. These studies also establish the concept that an antiarrhythmic agent can act by selective depression of abnormal cardiac cells forming parts of the re-entrant pathway at a concentration that has no effect or even a mild enhancing effect on electrophysiologic properties of normal cardiac cells. Our results point clearly to the potential pitfall of a long practice in basic as well as clinical studies on the actions of antiarrhythmic agents where data obtained from normal cardiac tissues were extrapolated to the pathologic situation. Thus, there is currently no basis to substantiate the concept that both DPH and lidocaine can abolish re-entrant rhythms by improving conduction in the re-entrant pathway, based on the fact that these drugs were shown to occasionally enhance the electrophysiologic properties of normal cardiac cells. This concept was previously doubted by those investigators who showed that both DPH and lidocaine can have quinidine-like depressant properties on cardiac cells in the presence of a higher potassium concentration. However, these studies fall short of emphasizing the fundamental difference in the action of DPH and lidocaine in pathologic versus normal cardiac cells.

The ionic mechanisms for the selective depressant effect of lidocaine and DPH in ischemic cells and potassium-depolarized cells are still largely conjectural. Our preliminary in vitro studies suggest that ischemia may result in depression of the fast Na channel and that lidocaine and possibly DPH may act by further impairment of this channel. Our observations should provide an impetus for further studies not only in terms of the different ionic conductance changes produced by antiarrhythmic drugs in normal and pathologic cardiac cells but also of the nature of these ionic abnormalities in pathologic situations such as acute, subacute or chronic ischemia.

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