Interactions between antiarrhythmic drugs and cardiac memory

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Abstract

Objective: Ventricular pacing or arrhythmias can induce cardiac memory (CM). We hypothesized that clinically administered antiarrhythmic drugs alter the expression of CM, and that the repolarization changes characteristic of CM can modulate the effects of antiarrhythmic drugs.

Methods: We studied conscious, chronically-instrumented dogs paced for two 1-h periods to study the effects of drugs on the evolution of memory (protocol 1) or for 21 days (protocol 2) to observe the effects of steady-state memory on drug actions. Dogs were treated in both settings with quinidine, lidocaine or E4031, in random order, and within therapeutic serum concentration ranges.

Results: Pacing, alone, for 2 h significantly prolonged ERP only near the left ventricular pacing site, whereas pacing alone for 21 days prolonged ERP at all sites (P<0.05). Quinidine and E4031, but not lidocaine, prolonged repolarization and ERP and suppressed evolution of CM in protocol 1. However, quinidine’s effect in prolonging repolarization was diminished in both protocols, while its effect in prolonging ERP was diminished in the 21-day protocol only. In contrast, the effects of E4031 were additive to those of CM, prolonging repolarization and ERP in both protocols, while lidocaine showed no changes in effect at all.

Conclusions: Pacing to induce CM significantly affects ventricular repolarization and refractoriness, and there are interactions between CM, quinidine and E4031. Depending on the specific drug, these interactions have the potential to be anti- or proarrhythmic, and may impact importantly on the clinical efficacy of drugs as well as on electrophysiologic testing of drug actions.

Keywords: Antiarrhythmic agents; ECG; K-channel; Ventricular arrhythmias

1. Introduction

Antiarrhythmic agents often manifest inconsistent antiarrhythmic and proarrhythmic effects in individual patients and groups of patients during acute or chronic drug administration [1]. Moreover, inconsistency in drug response has reduced confidence in the utility of programmed electrical stimulation to predict subsequent clinical benefit. A variety of explanations for this unpredictability have been identified, including variations in drug metabolism and plasma levels, use-dependent and reverse use-dependent actions of individual drugs, and progression in the primary diseases that underlie the arrhythmia [1].

Although these determinants of unpredictability are important, each can to some extent be anticipated and/or corrected for in treating individual patients. Yet, additional mechanisms might contribute to the unpredictability of drug effect. One such mechanism is the effect of ventricular arrhythmias to induce cardiac memory, defined as a T wave change occurring during sinus rhythm that tracks the QRS vector of previous ventricular paced or arrhythmic beats [2,3]. Cardiac memory is associated with functional alterations in the transient outward potassium current, Ito.

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[4] and possibly other ion channels [5,6], and with an altered voltage–time course of repolarization in ventricular myocardial cells [7]. It is suppressed by blocking \( I_{\text{Kr}} \) in anesthetized dogs [8].

It is also recognized that the binding to and unbinding of drugs from ion channels is importantly influenced by channel state (open, inactivated and resting), and that the function of ion channels is closely related to the voltage–time course of repolarization [1,9]. Based on the above, and because of the altered voltage–time course of repolarization in cardiac memory, we have hypothesized that antiarrhythmic drugs may alter the evolution of memory, and that the electrophysiologic changes accompanying cardiac memory may modify the expression of drug effect on ventricular repolarization and refractoriness.

2. Methods

All studies were performed on chronically instrumented, conscious dogs using protocols approved by the Columbia University Institutional Animal Care and Use Committee. We studied the effects of antiarrhythmic drugs administered to maintain a narrow range of plasma concentrations on evolution of cardiac memory using a protocol incorporating 2 h of ventricular pacing (referred to as protocol 1). As will be shown in Fig. 2, this protocol produces non-steady states of memory and of repolarization changes. This protocol was also considered a surrogate for changes in drug–cardiac interactions that might occur during arrhythmias of recent onset and/or during programmed electrical stimulation.

To study the actions of cardiac memory on the electrophysiologic manifestation of drug effects, we performed 21 days of pacing (referred to as protocol 2). This protocol provides a steady state of memory and of repolarization changes [7]. It was also considered a surrogate for pharmacologic intervention in the setting of a chronic cardiac arrhythmia.

We studied two highly selective drugs: lidocaine which blocks fast inward and plateau sodium currents [1,9], and E4031, which blocks the rapidly activating component of the delayed rectifier potassium current, \( I_{\text{Kr}} \) [10,11]. We also studied quinidine, whose actions to block \( I_{\text{Kr}} \) are accompanied by blockade of fast inward Na\(^+\) current, inward Ca\(^{2+}\) current, and \( I_{\text{in}} \) [1].

2.1. Surgical preparation

A total of seven dogs weighing 25–30 kg were prepared as previously described [7]. Under anesthesia and using sterile techniques, a unipolar pacing lead (Medtronic model 6917) was attached to the posterolateral left ventricular (LV) epicardium. The lead was connected to a programmable pacemaker (MINIX 8340, Medtronic), placed in a subcutaneous pocket. Platinum bipolar electrodes were sewn to the epicardium of (i) the left atrial appendage (LAA), (ii) the right ventricular (RV) free wall, and (iii) the anterobasal, (iv) apical and (v) inferior LV. These were used to pace or to measure activation–recovery intervals (ARI) as previously described [12]. The posterolateral electrode was located ~2 cm from the pacemaker lead. The animals recovered for 2–3 weeks, during which the ECG stabilized and they were laboratory trained.

Experiments were performed on conscious animals resting quietly on the right side. A pseudo-orthogonal three-lead ECG (I, aVF, v10) and the epicardial electrogram recordings were acquired at a 1000-Hz sampling rate using Ponemah software (Gould Instrument Systems) and the Dr Vetter PC-EKG program [7]. Frontal plane vector images were plotted with the Dr Vetter PC-EKG program.

For each experimental time point, three to five consecutive cycles of the three pseudo-orthogonal ECG leads were averaged, and the first derivative of the QT complex was plotted. Time between maximal deflections of the derivative at the beginning (positive) and end (negative) of the QTST complex were considered to define the QT interval. ERP were measured by stimulating each epicardial site separately using a nine-beat train of S1 (2-ms duration, 2× threshold amplitude) at BCL=500 ms. Diastole was scanned with the ninth beat after which there was a pause of 3 min before the next train. The longest S1–S2 interval failing to propagate defined the ERP. ERP/ARI relationships were calculated as indicators of alteration in antiarrhythmic effects.

Cardiac memory was quantified as a function of amplitude and angle changes of the T wave vector and expressed as displacement (in mV) between frontal plane T vector peaks during atrial pacing at baseline and after memory induction (Fig. 1). To test whether frontal plane recordings gave the same information as those from \( x \) and \( z \) planes we made simultaneous frontal plane (Dr. Vetter PC-EKG system) and \( xyz \) loop recordings (MIDA 1000, Ortivus Medical Systems, Sweden) in five dogs over 21 days. Vector quantification was identical in both systems.

2.2. Protocol 1: 2 h of pacing to study evolution of cardiac memory

A total of five animals were equilibrated during atrial pacing (the sinus rhythm surrogate) at CL=500 ms for 15 min. ECG, electrograms and ERP were recorded and a control blood sample drawn. Then, drug or placebo infusion was started (see below) and atrial pacing was continued for 30 min. Electrophysiologic measurements were repeated and another blood sample was taken. Then, to induce cardiac memory, a 60-min period of pacing from the posterolateral LV lead at CL=400 ms was performed, followed by 20 min of atrial pacing at CL=500 ms (recovery 1; Fig. 2, horizontal axis). A second ventricular pacing period was followed by a second 20 min of atrial...
different days as above. On the day each drug was investigated, pacing was discontinued for ~4 h to permit performance of the study. As we have shown previously [7], memory does not decline over such brief periods. To maintain memory at a constant level [4,7], on days between drug studies pacing was continued for 23 of each 24 h until all drugs had been studied.

No parallel study of a group of animals instrumented and not paced was performed as a control. However, in an earlier study [7] we incorporated a group of dogs paced from the atrium in a manner comparable to the ventricular pacing used to induce cardiac memory. In this group, no significant change in the ECG and VCG was seen over the time course of the study.

2.4. Drug administration

Quinidine was purchased from Sigma (St. Louis, MO) and lidocaine from Schein Pharmaceuticals (Florham Park, NJ). E4031 was a gift from Helopharm-W. Petrik (Berlin, Germany). Vehicle and placebo control was 0.9% NaCl (Baxter Healthcare, Deerfield, IL). Intravenous drug administration schemes were derived from the literature [12–14] and adjusted to produce stable ECG effects without significant side-effects. For quinidine we administered a 2-mg/kg bolus followed by a 0.07-mg/kg per min infusion. For E4031, the bolus was 50 mg/kg and the infusion 5 mg/kg per min. For lidocaine the bolus was 5 mg/kg and the infusion 0.2 mg/kg per min.

After each experiment, serum was separated and stored at −20°C until assayed. Drug levels were determined by HPLC after extraction [12]. HPLC solvents were purchased from Burdick and Jackson and other solvents and chemicals from Fisher Scientific. Quinidine was assayed using quinine as the internal standard [12]. E-4031 was quantified per Hashimoto et al. [13] using N-[3-[(1-3-(4-pyridinyl)propyl]-4-piperidinyl]carbonyl]phenyl]methanesulfonamide dihydrochloride (Wako) as the internal standard. Lidocaine levels were quantified using the modified method of Angelo et al. [15], with disopyramide as the internal standard.

2.5. Statistics

Data were analyzed using two-way repeated measures ANOVA to estimate drug and memory effects and their interaction. Subsequent analysis was done using the Bonferroni test where variances were equal and Games-Howell where variances were unequal. When analyzing influence of only one factor on a dependent variable, we used one-way repeated measures ANOVA. For control values in all studies, n=10 (five dogs in two sets of drug studies, with two different control values). For drug groups n=5 except for quinidine in long-term memory where n=4 (in one dog serum quinidine level increased to 9 μg/ml. Although this animal is not included in the overall group,
Fig. 2. (A) Pacing protocol (see horizontal axis) and effect of antiarrhythmic drug infusion on T wave displacement during short-term cardiac memory protocol. *P<0.05 compared to first recovery period. In addition, black symbols differ significantly (P<0.05) from comparably timed white symbols. ●, Control; ■, lidocaine; ▽, quinidine; △, E4031. (B) Representative experiment: modification of short-term memory by quinidine. Upper panels: frontal plane T wave vector projection during placebo control experiment. Lower panels: interaction of short-term memory and quinidine in the same animal. Left panels: baseline T vectors in control (upper) and 30 min after start of quinidine infusion (lower). VP1 and VP2 represent paced QRS and T wave vectors during first and second 60-min runs of ventricular pacing, respectively. In control (upper panels) recovery 1, there is an initial change in T vector at 0 min that subsequently decays. In recovery 2, the change is more marked and accumulates. Quinidine (lower panels) suppresses memory and its accumulation. Crosshair size, 0.5×0.5 mV.
its experimental result was identical). Data are presented as mean±S.E.M. P<0.05 was considered significant.

3. Results

3.1. Drug concentrations

Serum quinidine levels (µg/ml) were 2.1±0.4 and 3.0±0.4, respectively, before and after ventricular pacing in protocol 1, and 2.0±0.3 and 3.6±0.9 at the start and end of protocol 2 (all P>0.05). Serum lidocaine levels (µg/ml) were 3.2±0.4 and 2.0±0.3 for protocol 1 and 3.9±0.2 and 2.9±0.7 for protocol 2 (all P>0.05). Serum E4031 levels (ng/ml) were 55±11.2 and 104±15.7 for protocol 1 (P<0.05) and 71±21.3 and 84±11.6 (P>0.05) for protocol 2. The variation in E4031 concentrations in protocol 1 was not expected to affect results, as the cumulative i.v. administration of 100–1000 µg/kg of E4031 has been shown to alter equivalently the ERP, QTc and paced QT intervals [16]. In our experiments the range of cumulative E4031 doses was far smaller, only 170–250 µg/kg.

3.2. Protocol 1

This protocol tested the evolution of cardiac memory and whether the drugs administered altered this process. The time courses of cardiac memory accumulation and dissipation in drug-free controls are shown in Fig. 2A. In the drug-free, control state there was T vector displacement from baseline, which decayed during recovery 1. The second pacing period led to greater T vector displacement and greater accumulation (i.e. at any time during recovery 2, the extent of displacement was greater than in recovery 1). This accumulation of T wave changes typifies cardiac memory [3,7]. Both E4031 and quinidine markedly suppressed memory whereas lidocaine did not. Fig. 2B is a representative experiment, demonstrating the effects of quinidine.

3.2.1. QRS and QT changes

Measurements were made during atrial and LV pacing. No significant effects on QRS duration of atrially paced complexes were observed with any drug. During pacing alone or during pacing in the presence of lidocaine there was no significant change in the QT interval. The QT interval during pacing was prolonged by E4031 (P<0.05) and to a lesser extent, quinidine (P<0.05) (Fig. 3). During recovery periods the QT prolongation induced by E4031 was transiently reduced, while that induced by quinidine was reduced persistently. Hence, the effect of quinidine to

![Fig. 3](https://academic.oup.com/cardiovascres/article-abstract/50/2/335/274226/fig3){fig3.png}
increase the QT interval during control was reversed during the evolution of memory.

3.2.2. ERP changes

In the absence of drugs, ERP prolongation was seen only near the LV inferior wall site of primary ventricular pacing. E4031 and quinidine prolonged ERP at all sites. Data for the LV inferior site are presented in Fig. 4. Note that despite the suppression of memory by both drugs (Fig. 2A) and the alteration in QT interval (Fig. 3), ERP prolongation persisted after pacing. Lidocaine had no effect here (data not shown).

3.3. Protocol 2

This protocol tested whether antiarrhythmic drug action was altered in the setting of cardiac memory. At 7 days of ventricular pacing, and in the absence of drugs, T wave vector displacement was 0.54±0.12 mV. At 14 days, displacement increased to 0.74±0.16 mV (*P<0.05) and did not change thereafter (0.74±0.07 mV at 21 days). T wave vector amplitude and angle also changed significantly (data not shown). Given the profound alterations in the T wave vector in the setting of memory, we measured ARI in protocol 2 to provide information about local changes in repolarization associated with memory and to test the effects of drugs. No significant changes occurred in ARI as a result of pacing alone except for a decrease measured at the RV site (the farthest) at 14 and 21 days of pacing (Fig. 5A). The decrease in ARI at the farthest site correlated well with the evolution of cardiac memory, seen as T vector displacement (Fig. 5B).

3.3.1. QRS and QT interval changes

QT intervals during atrial and ventricular pacing were prolonged in protocol 2 (Table 1). Lidocaine and E4031 had no effect on the QRS complex, while quinidine increased QRS duration significantly. Effects of all drugs on the QT interval differed after 21 days as compared to control measurements (Table 1). Lidocaine lost its effect to decrease the QT interval. More importantly, E4031, which had prolonged the QT interval initially, prolonged it even more (during atrial pacing) after 21 days of pacing to induce memory. In contrast, quinidine’s effect to prolong the QT interval during atrial and ventricular pacing prior to performing the 21-day protocol was reduced following induction of memory.

3.3.2. ARI and ERP changes

At all stimulation sites prior to drug administration, ERP was prolonged significantly irrespective of whether ARI at the local site had increased or decreased (Fig. 6A). This suggests a disassociation of pacing effects on ERP and repolarization. Moreover, pacing to induce cardiac memory increased the dispersion of both ERP and ARI. These actions were not modified by lidocaine (data not shown). Whereas E4031 significantly and equivalently prolonged ERP and ARI before and after memory induction (Fig. 6B), quinidine (Fig. 6C) significantly increased ERP and ARI during control, but not after the 21-day protocol to induce cardiac memory.
4. Discussion

This study focuses on relationships between a complex physiological system (determining cardiac memory) [2,5,7] and three antiarrhythmic drugs: lidocaine, an I_{Na} blocker [1,9], E4031, a predominant I_{Kr} blocker [10,11], and quinidine, which blocks inward Na^{+} and repolarizing K^{+} currents [1] in conscious animals. Both protocols used to induce cardiac memory are similar to those we have previously standardized [4,7,8,17]. Based on our prior observations [8,17] we had predicted that in the 2-h protocol there would be a change in the T wave reflecting evolution of cardiac memory but not in the QRS or QT intervals. Both the I_{Kr} blocker, E4031 [10,11], and quinidine prevented memory from occurring, but lidocaine did not. This complements our earlier findings in open-chest, Table 1

<table>
<thead>
<tr>
<th>ECG interval (ms)</th>
<th>Pacing</th>
<th>Before VP to induce CM</th>
<th>After 21 days of VP</th>
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<tr>
<td></td>
<td>Control</td>
<td>Drug</td>
<td>Memory</td>
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<td>No drug</td>
<td>Memory+drug</td>
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<tr>
<td>QRS</td>
<td>AP 50±3.1</td>
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<td>51±3.8</td>
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<td></td>
<td>VP 76±2.8</td>
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<tr>
<td>QT</td>
<td>AP 198±1.8</td>
<td>–</td>
<td>212±3.3*</td>
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<td></td>
<td>VP 210±3.7</td>
<td>–</td>
<td>218±3.9*</td>
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<td></td>
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<td>Lidocaine</td>
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<td>QRS</td>
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<td>50±4.7</td>
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<td></td>
<td>VP 76±2.8</td>
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<td>QT</td>
<td>AP 202±2.1</td>
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<td>VP 214±6.4</td>
<td>205±6.8*</td>
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<td>E4031</td>
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<td>QRS</td>
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<td>50±5.0</td>
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<td></td>
<td>VP 78±3.4</td>
<td>76±3.3</td>
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<td>QT</td>
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<td>235±8.1*</td>
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<td>VP 212±4.7</td>
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<td>Quinidine</td>
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<td>QRS</td>
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<td>QT</td>
<td>AP 201±2.3</td>
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<td>VP 207±6.0</td>
<td>220±4.9*</td>
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* AP, atrial pacing; VP, ventricular pacing.
1 P<0.05 compared to control; ^1 compared to drug before memory; ^ compared to memory.
anesthetized dogs and in isolated tissues that a drug blocking $I_K$ and $I_{no}$ (4-aminopyridine) suppresses memory, whereas an $I_{Na}$ blocker, lidocaine, has no effect [8,18]. Our results with E4031 and quinidine are consistent with roles for both $I_{no}$ and $I_K$ in memory induction, and suggest that drugs blocking these currents would suppress memory and/or prevent it from occurring.

Long-term pacing to induce steady state cardiac memory was associated with an increased QT interval. Given the effect of chronic pacing to increase epicardial and endocardial action potential duration [7], prolongation of the QT interval was not unexpected. The association of memory with reduced $I_{no}$ [4], and reduced Na/K pump current and altered $I_{Ca,L}$ kinetics (H. Yu and I. Cohen, preliminary data) favors a prolongation of repolarization as well.

4.1. Effects of cardiac memory on repolarization and the ERP

Short-term pacing in protocol 1 to induce memory was unassociated with QT interval changes. In contrast, the 21-day protocol saw a small but significant prolongation of the QT interval during both ventricular and atrial pacing. The ERP was prolonged near the primary left ventricular pacing site in the short-term protocol (by 5%), and at all sites in the long-term protocol (by 7%). That protocol 1 was associated with a locally prolonged ERP is not surprising, given reports on pacing-induced increases in ERP in dogs and in human subjects [19–21]. For example, dogs in complete heart block for 3–7 days, and then paced for 1 h from the LV apex at CL = 500 ms in an acute, open-chest study demonstrated significant QT and ERP prolongation [21]. In contrast, dogs in sinus rhythm showed only ERP prolongation [19]. Given the propensity of dogs with heart block to develop LV hypertrophy [21], it is likely that in the heart blocked dogs hypertrophy evolving in the 3–7 days prior to the acute study contributed to the repolarization changes. The relationships of these observations to our own are uncertain, however, as the animals we routinely study are not in heart block and have no cardiac hypertrophy [7].

The discordance between the effects of cardiac memory
on ARI and ERP, recorded at various local sites in the ventricle, is emphasized in Fig. 6, as is the change in antiarrhythmic drug effects seen before and after memory occurred. With memory alone, ARI shortened at a site (RV) far from the primary pacing electrode, shortened less at the LV apex and lengthened at the LV base (earliest activated of the three). Hence, the previously noted dispersion of ARI that characterizes pacing to induce cardiac memory [22] occurred in our experiments as well. However, despite the changes in ARI, the ERP at each local site lengthened. Given the decrease in ARI at the RV site, the magnitude of change in ERP verges on the generation of post-repolarization refractoriness, whose potential for preventing reentrant rhythms has received significant attention [23]. The ERP is determined both by the voltage–time course of repolarization (dependent on inward plateau currents carried by Ca and Na and outward currents carried by K) and by the recovery from inactivation of the fast inward sodium current I_{Na}. Since repolarization changes are variable depending on the site studied, it is possible that pacing to induce cardiac memory has an independent effect to prolong recovery from inactivation of I_{Na}, thereby explaining the consistently increased ERP.

4.2. Clinical implications

If we consider pacing as a surrogate for ventricular arrhythmias, then the observation that pacing to induce cardiac memory prolongs ERP more than repolarization leads to an interesting question; that is, do arrhythmias of unifocal origin and consistent activation pathway have an ‘antiarrhythmic’ component that circumscribes their expression? This question awaits testing. It also suggests that ventricular pacing, per se, may provide an antiarrhythmic benefit based on ERP prolongation (although the increased dispersion of ERP might be associated with proarrhythmia).

Our results with the I_{Na} blocker, lidocaine, and the I_{Kr} blocker, E4031, indicate no suppression of drug effect in the steady state setting of memory. If anything, for E4031, the drug effect was augmented. Whether this would result in increased antiarrhythmic or proarrhythmic actions of a drug — or both — is largely a matter for conjecture at present. There are data from clinical case reports that suggest I_{Kr} blockers might promote proarrhythmia in the setting of cardiac memory [24,25]. In particular, Havrankamp et al. [24] reported a case of d,l-sotalol-induced torsades de pointes in a patient following catheter ablation of an A-V bypass tract. The authors suggested the arrhythmia was possibly attributable to, and certainly associated with, cardiac memory. Hence, when contemplating administration of drugs having actions to prolong repolarization (such as I_{Kr} blockers) the presence of cardiac memory might be a cause for concern. However, this awaits definitive testing.

For drugs with effects on multiple ion channels exemplified by quinidine, there is further complexity in the interaction. Perhaps most disconcerting from a clinical perspective is the loss of effect of quinidine to prolong ERP and QT intervals despite the maintenance of steady-state plasma levels. This could lead to two problematic scenarios: (i) the assumption by a physician of the need for higher doses of drug (unless plasma levels are measured) and resultant drug toxicity; or (ii) the recurrence of the patient’s initial arrhythmia, but with an altered morphology (based on altered voltage–time course of repolarization). The latter event might mislead a physician to conclude that the patient is experiencing proarrhythmia rather than a recurrence of the initial arrhythmia.

Our findings also impact on the interpretation of clinical electrophysiologic testing of antiarrhythmic drugs, which has not had the consistent predictive function originally anticipated. The extent to which pacing during electrophysiologic testing induces memory that accumulates and modifies the actions of certain antiarrhythmic drugs may contribute to misinterpretation of drug effect. Moreover, a drug administered at one time, when a preexisting arrhythmia has induced a given expression of memory, may act very differently than the same drug administered at another time, when the expression of memory differs. Finally, because memory is associated with altered ion channel properties [4], and because drugs affecting specific ion channels have differing effects based on the extent of expression of memory, we can assume that the binding and unbinding of drugs to their target sites in channels are altered as memory evolves. This would contribute to the complex and apparently inconsistent interactions between drug and arrhythmia that are so often seen clinically.

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