Prolongation of the cardiac action potential and refractoriness (class III effect) is a potentially beneficial electrophysiological mechanism of action. However, this effect may be diminished or eliminated at rapid heart rates, so-called ‘reverse rate dependence’ of prolongation of repolarization.

Action potential duration normally shortens as heart rate increases, due to increases in outward repolarizing currents, and/or decreases in inward depolarizing currents. The assessment of the effect of drugs on action potential duration is complicated by inter-species differences in ionic currents mediating repolarization, heterogeneity within the heart in repolarizing currents, and differential effect of drugs in different species, during differing experimental conditions, and at different rates of stimulation.

In general, most drugs which predominantly block the IKr repolarizing current exhibit reverse rate-dependent effects on cardiac repolarization. Drugs or combinations of drugs which produce multiple ionic channel blocks and possibly those which block the IKs current, may be less prone to this potentially undesirable effect.

Key Words: Antiarrhythmic agents, refractory periods, rate dependence.

Introduction

In the last decade, an accumulating body of experimental and clinical evidence has suggested that antiarrhythmic drugs which prolong the refractory period by means of prolongation of the cardiac action potential duration (APD) (Vaughan-Williams class III effect) are beneficial in preventing the recurrence of clinically relevant human arrhythmias (for simplicity, ‘delaying repolarization’ and ‘class III effect’ will be used interchangeably). For example, small clinical trials have shown that prolongation of refractoriness prevents the electrophysiological induction and spontaneous recurrence of ventricular tachycardias[1–3]. However, recent large-scale clinical trials of d-sotalol and dofetilide (both of which prolong refractoriness by selectively blocking a single repolarizing current, IKs) have been disappointing in that they have not shown a reduction of sudden cardiac death or overall mortality in post-infarction patients presumed to be at risk for re-entrant ventricular arrhythmias[4,5]. Data from these large-scale clinical trials have highlighted the need to re-assess the validity of extrapolating from small trials or in-vitro studies to a larger clinical context.

It has long been observed that the electrophysiological effects of drugs with class III antiarrhythmic properties diminish at higher heart rates and during sympathetic stimulation (i.e. in the precise situations when clinically relevant arrhythmias are most prone to occur). This phenomenon has been most clearly documented for drugs that selectively block the rapidly activating component of the delayed rectifier potassium current, IKr. This loss of class III effect with increasing cardiac frequency has been termed ‘reverse rate dependence’[6,7]. The term distinguishes it from the opposite phenomenon of ‘positive rate dependence’, which refers to the increasing degree of conduction slowing due to sodium-channel block observed with class I antiarrhythmic drugs when stimulation rates are increased[8–10]. The phenomenon of attenuation of class III effect at rapid rates may represent a weakness for a strategy that uses agents which rely on a single ionic channel target or mechanism of action to achieve their class III effect[7].
This review will discuss the complex physiological processes underlying the rate dependence of APD and refractoriness, the interpretation of studies of the relationship between rate and repolarization in vitro and in vivo, the phenomenon of reverse rate dependence observed with class III antiarrhythmic drugs, and possible strategies to attenuate reverse rate dependence in the clinical use of class III antiarrhythmic drugs.

Physiological rate dependence

In healthy ventricular and atrial tissues, faster stimulation rates (tachycardia) lead to a physiological shortening of APD\(^{[11]}\). A number of different mechanisms that may contribute to this normal phenomenon have been hypothesized. These include incomplete deactivation of components of the delayed rectifier potassium current (\(I_{K1}\) and \(I_{Ks}\)) during the short diastolic periods\(^{[12]}\), an increase in outward current across the sodium-calcium exchanger (caused by an increase in intracellular calcium with increased heart rates)\(^{[13]}\), an increase in the inward rectifier (\(I_{K1}\)) repolarizing potassium current\(^{[14]}\), and decreases in the inward calcium current\(^{[15]}\). Physiological APD shortening is clearly desirable, as it allows complete recovery of electrical and mechanical function between contractions at high heart rates.

Courtemanche et al. developed a computer model of an atrial action potential based on recordings from human atrial myocytes\(^{[16]}\). This model suggests that rate-dependent inactivation of current carried through the L-type calcium channel (\(I_{Ca}\)), and incomplete deactivation of the delayed rectifier potassium current (\(I_K\)), are the main mechanisms by which atrial APD adapts to increases in rate. A role for \(I_{Ca}\) is supported by the fact that inhibition of this current abolishes rate adaptation of the human atrial action potential in vitro\(^{[17]}\).

The response of cardiac tissues to stimulation is dependent on their refractory state; this in turn not only depends on the APD but also on excitability. In other words, the refractory period of a cardiac cell or tissue is affected by both its active and passive membrane properties. As a consequence, refractoriness (the most important variable governing the ability of premature impulses to propagate throughout the heart and cause re-entrant arrhythmias) may be prolonged for longer than the APD itself. This phenomenon is called ‘post-repolarization refractoriness’, and has been shown to occur in the ventricle following therapy with procainamide, quinidine or amiodarone\(^{[17,19]}\). In addition to the effects of passive membrane properties and the net contribution of other currents to excitability, changes in heart rate itself in vivo lead to (or are caused by) changes in autonomic tone that in turn modulate the effects of rate\(^{[20,21]}\). These complexities make it difficult to extrapolate from individual drug effects on particular currents or APD in isolated cells to effects on refractoriness in the intact human heart. Block of any one current may lead to compensatory changes in other currents, emphasizing the need to study drug effects in whole tissues and in vivo in addition to studying drug effects on isolated currents.

Physiological adaptation of repolarization to a new rate is a time-dependent process with at least two components. The first component lasts for a few seconds, while the second component has a half-life of up to a minute or longer\(^{[22,23]}\), possibly reflecting the time course of changes in the sodium pump current\(^{[12]}\), or in sympathetic activity\(^{[20]}\).

Heterogeneity of action potential duration

Action potential duration is heterogeneous in both the atria and the ventricles. Atrial APD is highly heterogeneous, partly because of variations in plateau currents (in particular, \(I_{To}\) and \(I_{Ca}\))\(^{[16]}\). Adaptation to changes in rate in human atria depends on the baseline action potential morphology. Three different subtypes of human atrial action potentials were identified by Dawodu et al., namely ‘spike and dome’, ‘gradual repolarization’ and ‘triangular’\(^{[24]}\). The baseline APD at slow rates and the slope and shape of the APD/rate relationship differ between these subtypes.

In the ventricles, different cell types exhibit variations in the relationship between APD and rate. For example, mid-myocardial cells (M cells) have a longer APD than either sub-endocardial or sub-epicardial myocardial cells at slow rates. However, the APD of M cells shortens to a greater extent than sub-endocardial or sub-epicardial cells when the rate is increased\(^{[25]}\). This results in a relatively greater dispersion of repolarization across the myocardial cell layers at slow rates, compared with fast rates; this is also a normal gradient of repolarization duration from cardiac apex to base\(^{[26,27]}\). The longer APD of M cells appears to be due, at least in part, to a relative deficiency of \(I_{K1}\)-repolarizing current (probably \(I_{K1}\)) and may account for the greater sensitivity of M cells to APD lengthening by \(I_{K1}\)-blocking antiarrhythmic drugs\(^{[28]}\). Some studies, however, suggest \(I_{K1}\) and \(I_{Ks}\)-blocking drugs prolong APD homogeneously in all myocardial cell layers\(^{[29]}\).

Heterogeneities in repolarization and the differing pharmacodynamic effects of drugs on different cell types may partly explain the tendency for repolarization-prolonging agents to provoke malignant arrhythmias. In the phenomenon of drug-induced torsade de pointes polymorphic ventricular tachycardia, for example, the pause that frequently precedes runs of tachycardia may cause excessive APD prolongation in some cells or tissues, leading to both afterdepolarizations and dispersion of recovery of excitability leading to re-entry.

Long-term changes in APD

Immediately after a change in rate, APD can shorten or prolong substantially from beat to beat, over the first
several beats. In addition to this short-term adaptation, recent work has focused on the effects of prolonged changes in rate. Prolonged (rather than short-term) changes in rate cause long-term adaptation of APD, a process that has been termed ‘electrical remodelling’. Wijffels et al. made the initial observation that APD shortened both in the short and long term after experimentally induced atrial fibrillation (AF) in goats. Since then, several clinical observations have corroborated their finding that AF of only a few minutes duration can shorten the atrial effective refractory period (ERP) by up to 30 ms, an effect that can persist for up to 8 min after spontaneous cessation of AF. The electrical remodelling is inhomogeneous, leading to an increase in the heterogeneity of ERPs after rapid atrial pacing, and thus to an increase in the inducibility and duration of experimental AF. These variable and long-term changes in APD with rate imply that the effect of antiarrhythmic therapy may be modulated by recent and remote heart rate history.

After cardioversion in patients with long-standing AF, steady-state atrial APD is substantially shortened (compared with control) at an atrial cycle length of 800 ms, and is largely unchanged at an atrial cycle length of 250 ms, indicating a marked shortening of the APD/rate relationship. In a canine model of AF, acute and long-standing shortening of APD, and an altered APD/rate relationship were found to result primarily from a reduction in $I_{Ca}$ as well as a reduction in $I_{Kr}$ repolarizing current. In keeping with this experimental observation, verapamil (but not propranolam, propafenone, propranolol, d-sotalol, or amiodarone) was able to attenuate the acute APD shortening caused by inducing AF in humans with normal atria and no previous history of AF. The clinical relevance of acute or long-term calcium channel block or the prevention of atrial electrical remodelling by other means is not clear and has not been the subject of clinical trials.

Information about electrical remodelling in the ventricles is limited. In autonomically intact dogs, after induction of 15 s of ventricular fibrillation, or very rapid burst pacing to the limits of refractoriness, the ventricular APD is substantially shortened, and recovers towards baseline with a biexponential process that has a terminal half-life of several minutes. As in the atrium, APD and refractory period changes in the ventricle substantially outlast the period of rapid rate, reflecting the kinetics of restoration to baseline APD.

**Interpreting experimental studies of rate dependence of drug effect on APD**

Although most experimental studies relating APD to rate focus on the relationship after single premature beats (the ‘electrical restitution curve’), or after many beats of stimulation to a ‘steady-state’ condition, it is probable that most human re-entrant arrhythmias are established after several initiating beats. While the precise initiating mechanism of ventricular tachycardia or AF (the most common clinical arrhythmias in humans) is not well understood in many patients, such arrhythmias can be initiated reproducibly in the electrophysiology laboratory by properly timed multiple ventricular or atrial premature stimuli. The necessary conditions for functional block and re-entry are thus established after several premature beats, probably reflecting block in some (although not all) adjacent regions of the myocardium, due to the regional dispersion of recovery of excitability. Re-entry phenomena can result from a differential adaptation in different myocardial regions to a sudden change in rate over a few beats, and thus reflect the kinetics of the APD/rate relationship at the onset of rate change, as well as the slope of the relationship at steady state. As a consequence, the measurements of the effects of drugs on the steady-state APD/rate relationship may be less important measures of the dynamics of drugs on refractoriness than the effects of drugs on APD within a few beats of rate change.

The effect of a particular rate of stimulation on APD is also dependent on the nature of the experimental model. Isolated membranes or cells studied in vitro allow the detailed dissection of the contribution of individual ionic currents that are responsible for changes in APD. However, in-vivo alterations of refractoriness will also depend on passive membrane properties determined by intercellular connections and tissue geometry, as well as haemodynamic, ischaemic, neurohumoral and autonomic factors, which will modulate the effects of changes in individual ionic currents. Experimental studies have been conducted on several animal species that may have different repolarizing currents from humans, especially with respect to the relative density of the various repolarizing potassium currents (e.g. $I_{to}$, $I_{Kr}$).

The interpretation of drug effects both in vitro and in vivo is also complicated by differing experimental models, doses of antiarrhythmic drugs, and the rates and durations of stimulation. For example, the phenomenon of rate dependence of repolarization is often studied over a limited range of heart rates after short periods of stimulation. In the intact heart, clinically relevant ventricular and atrial arrhythmias often occur at very high rates (e.g. >200 beats.min$^{-1}$) and last for prolonged periods. In addition, atrial and ventricular frequency-dependence profiles are not necessarily related for many drugs that prolong APD. There may be important species differences in current densities which complicate the evaluation of antiarrhythmic drugs. For example, rabbit ventricular cells have little or no $I_{Kr}$; in dog ventricular muscle, $I_{Kr}$ is present but in some studies plays little role in repolarization at slow or fast cycle lengths, whereas $I_{Kr}$ may be a more important component of total repolarizing current in guinea pigs and man.

Importantly, the results in some studies are expressed as absolute changes in refractoriness for a given cycle length, and in others as relative changes in
refractoriness. As the APD and refractory periods normally shorten with increases in frequency or rate, drug effects are more properly described as deviations from the normally expected shortening of APD with increase in rate. For example, if a drug attenuates the normal shortening of APD observed with rate increases, then the proportional drug effect will increase as the rate increases (positive rate dependence), even if the action potential itself shortens as the rate increases. Conversely, where the APD shortens with a steeper slope than occurs before drug therapy, the proportional change in APD with increases in rate will become smaller or be obliterated (reverse rate dependence). As it is plausible to expect drug effects to be related proportionally to the baseline value of APD, a comparison between studies is made easier by expressing the changes as a proportion of baseline APD or ERP (i.e. as a percentage change) rather than as absolute changes in these variables. These different theoretical patterns of APD, rate relationship are illustrated in Fig. 1.

**Antiarrhythmic drugs delaying repolarization and rate dependence of effect on APD and refractoriness**

**Animal experiments**

In most in-vitro experimental systems, the majority of selective blockers of I_{Kr} exert reverse rate-dependent effects on APD, with a loss of effect at very rapid stimulation frequencies\[^{29,43,44}\]. Agents of this type include \(\beta\)-sotalol, dofetilide, ibutilide, E-4031 and WAY-123,398. Original observations of the reverse rate-dependent effects of dofetilide on APD were ascribed in part to a rate-dependent, incomplete deactivation of I_{Ks} with increases in rate, leading to relative increases in I_{Ks}; as these I_{Ks} repolarizing effects were not blocked by dofetilide, they counteracted the effects of dofetilide on APD at rapid rates\[^{29,44}\]. It was therefore suspected that I_{Ks} blockade could prevent reverse rate dependence. In other studies, however, I_{Ks} contributes little to total repolarizing current at slow or fast rates, suggesting increased I_{Ks} as heart rate increases may not be the explanation for rate-dependent APD shortening\[^{40}\]. Although the potential mechanisms of rate dependency of I_{Ks} block on APD are not well understood, selective block of I_{Ks} by chromanol 293B results in APD prolongation in guinea pig and human ventricular cells that is independent of rate\[^{29,41}\], in contrast to the effect of dofetilide, whose APD-prolonging effects were amplified at slow rates and strongly attenuated at frequencies of 2–4 Hz\[^{41}\].

In a study of guinea pig papillary muscle, dofetilide (a selective blocker of I_{Ks}) exerted reverse rate-dependent effects on APD with both normal and elevated extracellular potassium concentrations; in contrast, the effect of ambisalide (a blocker of both I_{Ks} and I_{Kr}) was preserved as the stimulation frequency was increased from 0.5 to 3 Hz, regardless of potassium concentration\[^{45}\].

Azimilide, which blocks both I_{Kr} and I_{Ks}, has been reported to have reverse rate-dependent effects on APD in guinea pig and ferret papillary muscles\[^{42,46}\]. In contrast to the in-vitro setting, in-vivo studies have shown that the effects of azimilide are rate independent. For example, in a dog model of AF, the effect of azimilide on ERP was rate independent when tested at 400 and 200 ms cycle lengths. In contrast, in the same model, the effect of dofetilide was reduced at faster rates\[^{47}\].

The actions of drugs with less selectivity for a particular repolarizing current are more complex. For example, RP58866, a drug that blocks I_{Kr} and I_{Ks}, exerts slight reverse rate-dependent effects on ventricular ERP\[^{43}\].

The effect of \(\beta\)-adrenergic stimulation on the frequency-dependent actions of class III agents has been studied by Schreieck et al.\[^{48}\]. \(\beta\)-adrenergic stimulation increased I_{Kr} activity, but had no effect on I_{Ks}. Stimulation of \(\beta\)-adrenergic receptors with isoproterenol alone shortened APD in isolated guinea pig papillary muscles, but did not change the APD/rate relationship. Isoproterenol at higher doses (100 nmol.1\(^{-1}\)) eliminated the action potential prolongation effect of dofetilide, and steepened the APD/rate relationship such that the APD was shortened at

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rapid rates but was unaffected at slower rates. In contrast, ambisilide (which blocks both \( I_{Kr} \) and \( I_{Ks} \)) prolonged APD with no change in the slope of the APD/rate relationship; with the addition of isoproterenol, APD was shortened but the APD/rate relationship remained the same as that with ambisilide alone. With chromanol 293B, there was a small rate-independent increase in APD that was accentuated by the addition of isoproterenol. However, both early and late after-depolarizations were observed following chromanol 293B and isoproterenol, which were not seen in the control situation and were infrequent during dofetilide administration\[^{[48]}\].

**Clinical studies**

As in animals, ERP and APD in humans shorten with increases in rate and with reductions in diastolic intervals for single premature beats (time-dependent electrical restitution). Although intracellular APD cannot be recorded in humans in vivo, the extracellular monophasic action potential (MAP) measured from a population of about 50–100 cells with a contact electrode catheter has been validated as a surrogate of the action potential of a single cell, with respect to APD duration\[^{[49]}\]. The availability of this technically uncomplicated surrogate measure of APD has led to widespread investigations into the relationships between cycle length, drug therapy and MAP. Ventricular refractoriness and monophasic APD (MAPD) tend to parallel each other over a wide range of cycle lengths; however, there appears to be a slightly greater shortening of the MAPD than of refractoriness at short cycle lengths, leading to an increase in the right ventricular ERP/MAPD ratio (changing in humans from a value of 0.9 at a cycle length of 600 ms to 1.0 at 300 ms)\[^{[50,51]}\].

Studies of the relationship between rate and MAPD and/or refractory periods for various drugs in humans are summarized in Table 1. Most studies show reverse rate dependence in the action of \( I_{Kr} \) blockers at rates \(< 350 \text{ ms} \), whereas drugs with multiple ion channel block, in particular combined sodium and potassium channel block, are associated with attenuation of reverse rate dependence or have class III actions that appear to maintain their effects at high rates. Although drugs that appear relatively selective for the blockade of \( I_{Kr} \) or \( I_{Ks} \) provide both sodium- and potassium-channel block, in particular combined sodium and potassium channel block, are associated with attenuation of reverse rate dependence. As blockade of the slowly activating \( I_K \) repolarizing current \((I_{Ks})\) appears to result in no reverse rate dependence in vitro, it is possible that combining \( I_{Ks} \) block with \( I_{Kr} \) block in humans may also result in the attenuation of reverse rate dependence.

Amiodarone is an investigational class III antiarrhythmic agent which blocks both \( I_{Kr} \) and \( I_{Ks} \). To date, no clinical studies have examined the effects of amiodarone on refractoriness at varying rates in detail. Catecholamine stimulation via isoproterenol significantly increases \( I_{Ks} \) in guinea pig myocytes sufficiently to completely reverse the effects of the potent \( I_{Kr} \) blocker E-4031\[^{[56]}\]. On the other hand, azimilide was able to resist MAPD shortening induced by isoproterenol, presumably because of \( I_{Ks} \) blockade\[^{[57]}\].

In humans, the effects of sematilide on MAPD are reversed by isoproterenol, whereas the effects of amiodarone are only partially attenuated\[^{[55]}\]. This supports the clinical utility of adding beta-blocker to antiarrhythmic drug therapy with class III agents (even those that already have mild beta-blocking effects, such as amiodarone)\[^{[58]}\].

**Conclusion**

In summary, although there is some discrepancy between different studies, selective \( I_{Kr} \) blockers appear to initiate at least some degree of reverse rate dependence in their effects on ventricular MAPD and refractoriness in humans. Less selective potassium-channel-blocking drugs or combinations of drugs that provide both sodium- and potassium-channel block, appear to maintain their effects at high rates. Although drugs that appear relatively selective for the blockade of the \( I_{Ks} \) current in vitro are essentially rate independent (e.g. chromanol 293B), no such agents are currently available for human use.

Assuming that prolongation of refractoriness at rapid rates is a desirable antiarrhythmic property, selective \( I_{Kr} \) current block may not be as useful as less selective block of multiple potassium currents or even added sodium-current block. Excessive potassium-current block is associated with marked action potential prolongation

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<table>
<thead>
<tr>
<th>Author</th>
<th>Drug</th>
<th>Channel(s) blocked</th>
<th>Dose</th>
<th>Rates (ms)</th>
<th>Rate-dependent effects</th>
</tr>
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<tbody>
<tr>
<td>Sager et al. 1994[55]</td>
<td>Amiodarone</td>
<td>I_{Kr}, I_{Ks}, I_{Na}</td>
<td>1618 ± 32 mg . day^{-1}</td>
<td>500-300</td>
<td>Rate-independent MAPD and ERP prolongation</td>
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<td>Sager et al. 1993[18]</td>
<td>Amiodarone</td>
<td>I_{Kr}, I_{Ks}, I_{Na}</td>
<td>380 ± 162 mg . day^{-1}</td>
<td>600-300</td>
<td>Rate-independent MAPD prolongation</td>
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<td>Huikuri and Yli-Mayry 1992[68]</td>
<td>Amiodarone</td>
<td>I_{Kr}, I_{Ks}, I_{Na}</td>
<td>400 mg . day^{-1}</td>
<td>700-350</td>
<td>Rate-independent ventricular ERP prolongation</td>
</tr>
<tr>
<td>Naitoh et al. 1998[64]</td>
<td>DL-sotalol</td>
<td>I_{Kr}, BB</td>
<td>320 mg . day^{-1}</td>
<td>600-300</td>
<td>Rate-independent ventricular ERP prolongation</td>
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<td>Schmitt et al. 1991[65]</td>
<td>DL-sotalol</td>
<td>I_{Kr}, BB</td>
<td>1.5 mg . day^{-1}</td>
<td>600-300</td>
<td>Reverse rate-dependent MAPD prolongation</td>
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<tr>
<td>Sager and Behboodikhah 1996[51]</td>
<td>DL-sotalol</td>
<td>I_{Kr}, BB</td>
<td>362 ± 20 mg . day^{-1}</td>
<td>600-300</td>
<td>Rate-independent MAPD prolongation; reverse</td>
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<tr>
<td>Lee 1997[52]</td>
<td>DL-sotalol+quinidine</td>
<td>I_{Kr}, I_{Ks}, I_{Na}</td>
<td>150 ± 8 mg . day^{-1}</td>
<td>600-400</td>
<td>Rate-independent ventricular ERP and ventricular FRP</td>
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<tr>
<td></td>
<td>or procainamide</td>
<td></td>
<td>1337 ± 59 mg . day^{-1}</td>
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<td>prolongation</td>
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<tr>
<td></td>
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<td></td>
<td>2083 ± 327 mg . day^{-1}</td>
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<td>Sedgwick 1992[66]</td>
<td>Dofetilide</td>
<td>I_{Kr}</td>
<td>6 µg . kg^{-1}</td>
<td>800-500</td>
<td>Rate-independent MAPD and ventricular ERP</td>
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<td>Demolis 1996[67]</td>
<td>Dofetilide</td>
<td>I_{Kr}</td>
<td>0.75 mg . day^{-1}</td>
<td>1000-400</td>
<td>Reverse rate-dependent QT prolongation</td>
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<tr>
<td>Sager 1995[68]</td>
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<td>I_{Kr}</td>
<td>1.2 ± 0.4 mg . day^{-1}</td>
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<td>Reverse rate-dependent MAPD prolongation</td>
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<td>2 mg . kg^{-1}</td>
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<td>Reverse rate-dependent MAPD prolongation</td>
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<td>E-4031</td>
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<td>9 µg . kg^{-1}</td>
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<td>Reverse rate-dependent right ventricular ERP prolongation</td>
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<td>Reverse rate-dependent right ventricular ERP prolongation</td>
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<td>I_{Kr}</td>
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MAPD=monophasic action potential duration; ERP=effective refractory period; FRP=functional refractory period; βB=beta-blocker.
and an increased incidence of torsade de pointes, and excessive sodium-channel block is associated with untoward conduction slowing and proarrhythmia. Excessive MAPD prolongation at slow rates and slowing of conduction at rapid rates must therefore be avoided, while attempting to preserve prolongation of refractoriness following the premature beats or short runs of tachycardia that often precede clinical ventricular tachycardia or ventricular fibrillation. Since adrenergic stimulation attenuates class III drug effects, beta-blockers would be expected to enhance the efficacy of any drug which prolongs action potential duration.

An understanding of the clinical relevance of action potential prolongation and its relationship to rate is complicated by our lack of in-depth knowledge of the complex spatial and temporal variability in recovery of excitability that is associated with clinical ventricular arrhythmias. Most particularly, it may not only be the magnitude of class III action that confers protection from re-entrant ventricular arrhythmias, but also the ability of drugs to prevent or alter the heterogeneity of ventricular electrophysiological properties that are the pre-conditions for re-entrant arrhythmias. Nevertheless, observations from clinical trials suggest that drugs with pure I\textsubscript{Kr}\textsuperscript{-} blocking properties, perhaps subject to reverse rate dependence, do not confer benefit and may even increase mortality in patients following myocardial infarction. In contrast, amiodarone (the only clinically available drug that attenuates reverse rate dependence) appears to have a modest benefit on sudden cardiac death, and perhaps overall mortality, in similar patients.

This review was supported by an educational grant from Procter & Gamble Pharmaceuticals.

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