

Myocardial Repolarization and Drugs Impossibility to predict the dominance of anti-arrhythmic over pro-arrhythmic effects of drugs due to differential and ventricular electrical remodeling

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It is known that application of anti-arrhythmic drugs for the acute treatment of arrhythmic can not only result in succesfull termination or prevention, but also can lead to unwanted pro- arrhythmic effects. On the basis of two arrhythmias, atrial fibrillation and Torsade de Pointes arrhythmias, we will highlight the relevance of differential atrial and ventricular electrical remodeling to explain the delicate and dynamic balance between anti- arrhythmic efficacy and pro- arrhythmogenic consequences of class III anti- arrhythmic drugs. (*Ana Kar Der, 2001; 1: 27-34*)

Introduction

Around 1970, Vaughan Williams suggested to list anti- arrhythmic drugs according to their predominant action in 4 categories (1). Classification was primarily based on tests performed under physiological circumstances: i.e. assesment of the effect of the durg on ionic currents or receptors of normal cells, tissues or animals. From the currently, clinically available anti- arrhythmic drugs it is known that they all have the potential to generate Pro- arrhythmia, defined as worsening of the existing arrhythmia or the appearance of a new arrhythmia at a dose which is not considered toxic (2).

Anti- arrhythmic drugs that prolong repolarization belong to class III (1). They achieve their action by bloacade of repolarizing currents, although we are aware that (a) a number of class a drugs, like quinidine and procainamide, can also lengthen QT-time and (b) representatives of the class III group, such as amiodarone and sotalol, have a much broader action than just action potential duration (APD) lengthening. Still we refer to all these drugs as class III in the remainder of this text.

The development of improved anti- arrhythmic therapy depends in large on detailed understanding of the

mechanisms for anti-and also pro- arrhythmic action. The search for new anti- arrhythmic in the late 80's was guided by the knowledge that multiple wave reentry plays an important role in the perpetuation of atrial fibrillation (and other (supra) ventricular tachycardias). Therefore much attention was given to drugs that could increase the wavelength, defined as the product of the conduction velocity and the refractory period (3) most particularly by increasing reporalization (class III action). However, more recent discoveries concerning time-dependent electrophysiologic and ultrastructural remodeling as a consequence of the arrhythmia (especially atrial fibrillation) were not considered. Indeed these pathophysiologic adaptations are not taken into account in the current designs of clinical drug trials.

To limit the size of this review, we will discuss two conditions to support our case: atrial fibrillation (AF), the most common clinically occurring arrhythmia, was selected in order to describe the efficacy of drugs as anti- arrhythmics. Acquired Torsade de Pointes arrhythmias (TdP) was chosen as a representative example for clinical pro- arrhythmia of class III drugs, which can become life-threatening and severely limits the use of these drugs today (4). We will demonstrate new aspects concerning the delicate and dynamic balance between anti- arrhythmic efficacy and possible pro- arrhythmic consequences within these conditions and discuss experimental and clinical evidence to better understand the underlying mechanisms.

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Anti-arrhythmic drugs and suppression of experimental atrial fibrillation

Large animal models of AF have been listed in table 1. With the development of chronic models, the potential role of the arrhythmia itself in the promotion, and continuation of AF became clear (5,6). Also on the basis of the etiology, e.g. mitral regurgitation, different adaptation processes can be anticipated. Depending on the model therefore, different forms of contractile, structural and electrical remodeling have been described (5-7). In the "AF begets AF" goat model or in the "rapid pacing induced AF" canine model, electrical remodeling consists of long term shortening of the atrial effective refractory period (AERP) which is most pronounced at slower rhythms resulting in a flat or inverse frequency dependency of the atrial APD. Subsequently, atrial fibrillation becomes more stable and the duration

Table 1: Animal models of AF

	Clinical Relevance	Sustained AF
1. Normal animals	-	-/+
2. Mitral regurgitation	+++	+
3. Sterile pericarditis	++	+
4. Vagal induced AF	+	+++
5. AF-induced AF	+++	+++
6. rapid pacing induced AF	++	+++
7. CHF induced AF	+++	+++

of AF episodes increases progressively (5,6). A decrease in conduction velocity has not consistently been described in "AF begets AF", but seems important in "rapid pacing induced AF" and is the sole contributor in "CHF induced AF" (5-7). The mechanisms underlying AF in the different models is therefore also quite different (table 2). In the "vagally induced AF", the shortening in AERP is physiological but not homogeneous causing an increase in spatial dispersion of repolarization and the possibility for numerous waves (8). As long as the cholinergic stimulation is maintained, atrial fibrillation will be present. Due to the very marked shortening in AERP (electrical remodeling), multiple very short waves can coexist in the "pacing induced AF" models (9). With time it becomes more difficult to terminate this fibrillation process. However, in "CHF induced AF" repolarization is normal, but conduction has slowed and become non-uniform, i.e. there is excessive dispersion of conduction due to fibrosis. This results in AF consisting of a macro-reentry circuit resembling atrial flutter (7). The different electrophysiological alterations in these models affect the (supposed) efficacy of drugs. The effects

found in vagally-induced AF (8) may not translate to the other forms of AF. Recently, it has become clear that the response of the drug is indeed dependent on the substrate or underlying mechanism (10): dofetilide iv. Has been shown to be very effective against CHF induced AF (100%: dose 10-80 mg/kg), partly effective against cholinergic AF (42-50%, dose 80-160 mg/kg), and not effective against rapid pacing induced AF (12.5%, 80 mg/kg).

Table 2: Mechanisms of AF

<p>1 CHOLINERGIC INDUCED AF</p> <ul style="list-style-type: none"> - ↓ AERP - Increased spatial dispersion in AERP - Initiation easiest at shortest AERPs - Numerous waves
<p>2 AF OR PACING INDUCED AF</p> <ul style="list-style-type: none"> - ↓ AERPs – electrical remodeling - ↑ spatial electrophysiological heterogeneity - (↓ conduction)
<p>3 CHF INDUCED AF</p> <ul style="list-style-type: none"> - = AERP - = electrical heterogeneity - ↑ interstitial fibrosis – ↓ conduction - macro-reentry (small number circuits) atrial flutter

Anti-arrhythmic efficacy for clinical atrial fibrillation

Numerous studies have evaluated the anti-arrhythmic efficacy of drugs to terminate AF either intravenously or orally (11-15). In the most recent trials with new class III drugs (dofetilide or ibutilide), the efficacy against atrial flutter was higher than against atrial fibrillation (12,15), a finding which could shed some light on the underlying mechanism when placed in the above context of the effects of dofetilide in the different animal models. In addition, the arrhythmia duration – and therefore time-dependent remodeling – is an important determinant of drug conversion (15): a long duration (months) almost completely precludes drug conversion. Similarly, time-dependent reversed remodeling appears to be clinically important: drugs previously ineffective may be applied successfully after (presumed) reversed remodeling was achieved (17). It must be kept in mind however that AF-induced electrical remodeling has not been proven yet in humans (18-21) and relies on postconversion reversal studies (22-25). At present it is not precisely known how conditions like atrial hypertrophy, dilatation, fibrosis or high atrial rate it-

self affect drug efficacy. In addition, these factors usually interact and their separate effects cannot be sorted out reliably in the clinical situation. Therefore, acute conversion regimens tailored to these specific pathophysiological conditions are not feasible yet.

Chronic prophylactic treatment is indicated for frequent paroxysmal as well as postcardioversion AF. Associated cardiac conditions, frequency of the attacks and duration all may affect drug efficacy. Especially in chronic AF time-dependent changes may affect success of postcardioversion drug prevention. Recently the types of postcardioversion AF have been further subdivided: (a) immediate postshock recurrence (IRAF), (b) subacute recurrence and (c) late-re-occurrences. Presumably, a dynamic anti-arrhythmic approach is warranted depending on time after cardioversion (26).

Electrophysiologic and ultrastructural adaptations and anti-and pro-arrhythmic drug effects

The electrical in vivo adaptations have been the subject of recent experimental molecular and cellular studies. Concerning ionic channels, the reduction in atrial APD has been associated experimentally with reduced contribution of I_{CaL} and I_{to} (27), whereas the conduction disturbance has been related to a decrease in I_{Na} (28) but also (heterogeneous) down-regulation of connexins (29) and dispersion of conduction (7). In humans, similar observations have been made for I_{CaL} and I_{to} (30,31). These observations are paralleled by a decrease in channel protein expressions (32).

In addition to electrophysiological changes, AF causes alterations in cellular ultrastructure and Ca -handling, which resemble the changes seen in hibernating myocardium (33), resulting in negative inotropy or complete absence of contractile function. Hibernation is compatible with the clinical observation that it takes some time before contractile function returns to normal when sinus rhythm is restored. How these alterations (and their reversal after restoration of sinus rhythm) affect drugs' actions is largely unknown at present.

These tachycardia-induced changes in ion channel functions affect anti-arrhythmic drug actions at the atrial level. The same holds however also for the ventricles. During chronic tachycardia electrical and ultrastructural ventricular adaptations also occur, either due to heart failure, hypertrophy or the tachycar-

dia itself. The net effect is not always predictable: these conditions may reduce or enhance ventricular anti-arrhythmic drug effects or even produce TdP.

Clinical evidence of pro-arrhythmia

A classic description of the fact that anti-arrhythmic treatment may produce pro-arrhythmic complications was presented by Selzer and Wray in 1964 (34). At first classified as self-terminating ventricular fibrillation it became clear that it was a polymorphic ventricular tachycardia in the presence of a prolonged QT-time, commonly referred to as TdP (35).

More detailed analysis from literature data revealed that TdP on the basis of anti-arrhythmic (drug induced prolongation of QT) occurs as a complication of anti-arrhythmic drug treatment in 1-5% of patients (12-15, 34,36-38). All class Ia (quinidine, procainamide) and class III drugs can cause TdP, both during (the attempt of) pharmacological conversion as well as during oral treatment to maintain sinus rhythm. TdP may occur as an idiosyncratic response in susceptible patients but seems to be especially frequent in patients with heart failure. This suggests that patients developing heart failure (e.g. during the course of the disease which also caused AF) at the same time may develop the electrophysiological conditions related to class III pro-arrhythmia (figure 1).

Experimental evidence for drug-induced pro-arrhythmia

Looking at data from animal models studying the sensitivity of class II drugs to induce TdP arrhythmias, we have to acknowledge the fact that ventricular electrical remodeling is an important pre-requisite for the occurrence of TdP. This knowledge came forward from studies using dogs comparing acute (AAVB) versus chronic AV-block (CAVB). At first, studies were initiated to elucidate the mechanisms involved in drug induced polymorphic ventricular tachycardia (39-42). Because bradycardia is one of the predisposing clinical factors for acquired TdP (together with hypokalemia / hypomagnesemia), interventions were aimed at slowing the rhythm: vagal stimulation, sinus node crush and AV-block. The bradycardia induced at AAVB leads to frequency dependent lengthening of ventricular APD (physiological adaptation), increases in ventricular end-diastolic pressures, and a fall in cardiac output. Application of the class III agent d-sotalol (2 mg/kg), however, does not result in spontaneous or pacing induced TdP at this early time point (42). However, repetition of the same protocol 5 weeks later (CAVB) re-

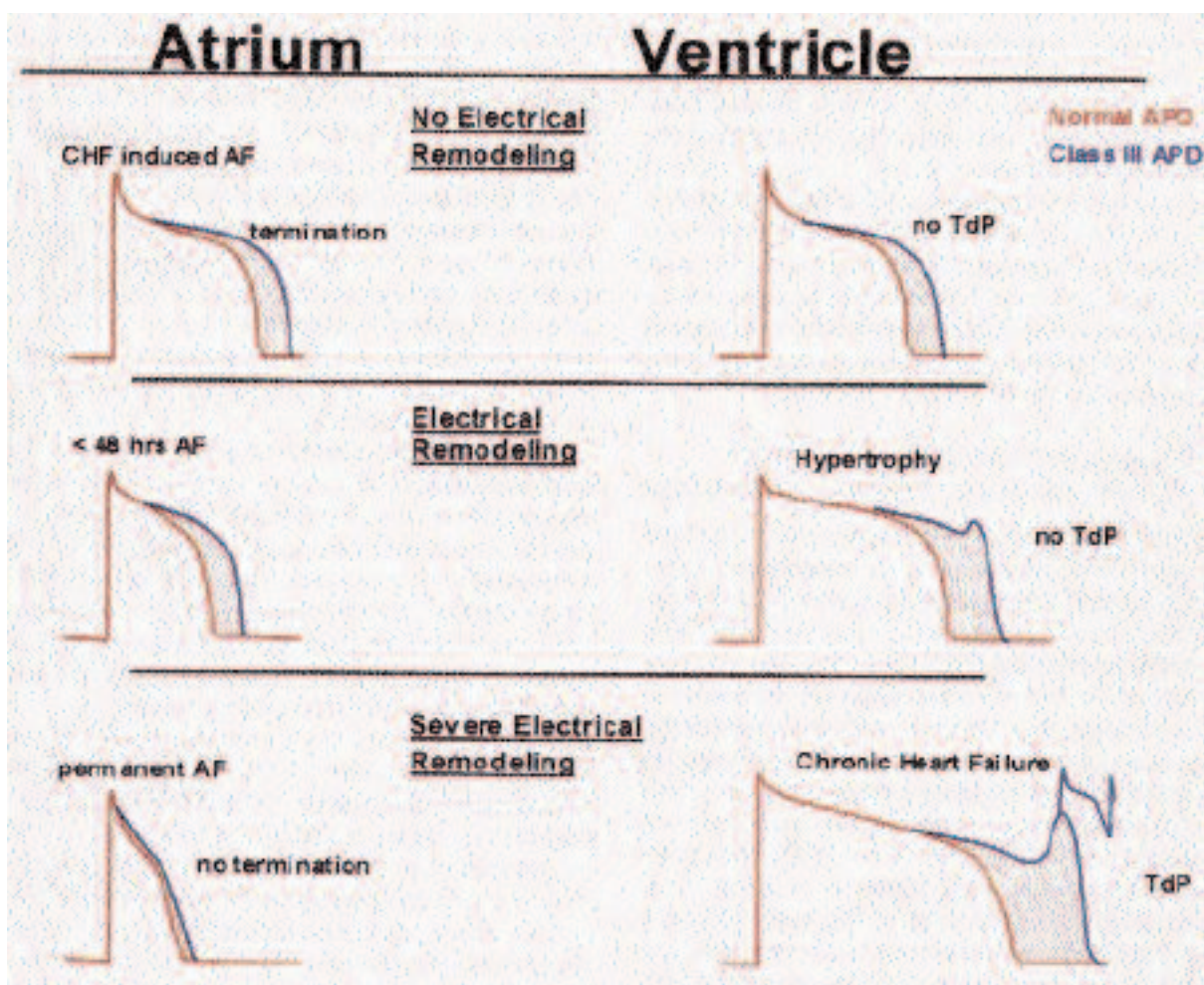


Figure 1: In this illustration 3 atrial (left part) and 3 ventricular action potentials are depicted representing 3 conditions of electrical remodeling: 1) no (upper part), moderate and severe electrical remodeling (lower part) before and after class III drug administration. Whereas the atria respond to AF with shortening of the APD (upper to lower left), ventricular electrical remodeling due to hypertrophy or heart failure is characterized by an increase in the repolarization times. The reverse use dependency of class III drugs is incorporated. Therefore pharmacological intervention to treat AF may lead to termination depending on the electrophysiologic atrial substrate. At the same moment, the lengthening in ventricular APD poses a risk for TdP arrhythmias. Especially in heart failure the anti-arrhythmic effect of a drug (termination of AF) may be accompanied by a pro-arrhythmic response (TdP).

sults in the induction of TdP in the majority of the dogs, although the severity of the bradycardia and/or the dose of d-sotalol are similar (42). Other studies have shown that to initiate TdP in dogs with sinus rhythm or AAVB requires higher concentrations of drugs (up to 4 times the dose of CAVB) indicating that predisposing factors should be present in the chronic dog model. This enhanced susceptibility has been associated with ventricular remodeling, including (a) electrical remodeling: marked non-homogeneous lengthening of the ventricular APD leading to more marked interventricular dispersion (40+35 ms at AAVB vs 70+30 ms at

CAVB), and an altered electrophysiological response to d-sotalol (no increase in dispersion at AAVB, 45+30 ms, versus a further increase in APD dispersion at CAVB, 125+65 ms); (b) contractile remodeling: marked increase in contractility (dP/dt max + 100%), and return of the end-diastolic pressures to pre-AV-block levels with an increased incidence of triggered ectopic beats when the cardiac function is potentiated, and; (c) structural remodeling: biventricular hypertrophy without fibrosis. All these findings have been confirmed at the cellular level (43-45). Moreover, patch clamping has revealed that the ionic remodeling is

predominantly related to changes in I_{K1} and NCX. In both ventricles I_{K1} is downregulated while NCX is up-regulated in both modes (44-45).

Thus, the lengthening in APD in the CAVB dog is the result of changes in ionic currents. Block of especially the currents responsible for repolarization by class III agents will affect the diminished strength of repolarization (decrease in repolarization reserve) further so that the pro-arrhythmic potential of these drugs is facilitated. The proposed mechanisms for acquired TdP include (a) a focal initiation through early after depolarizations which occur more readily in prolonged APDs and (b) perpetuation by reentrant activity that is precipitated by the very marked dispersion.

Balance between anti-arrhythmic efficacy and pro-arrhythmic consequence

Unfortunately, drug effectiveness and pro-arrhythmia seem to be related. In direct comparisons, (quinidine vs sotalol (14) or ibutilide vs sotalol (12), the more effective drug also showed a higher pro-arrhythmic potential. In the case of quinidine (14), this was associated with an increased precordial QT dispersion. Similar findings were obtained with the experimental drug almokalant (38). Certain clinical conditions may adversely affect the balance between anti-arrhythmic and pro-arrhythmic drug effects. The most important example is congestive heart failure (CHF), since it frequently complicates atrial fibrillation and vice versa. Patients with CHF have a higher risk to die suddenly. The underlying mechanisms are unknown, although an increase in the QT-time or in the ventricular APD has been described consistently. This predisposition for SCD could be related to drug-induced TdP. This concept is consistent with the observed increased mortality in patients with AF and heart failure treated with anti-arrhythmic drugs in the SPAF trial (37).

In figure 1, we have summarized our concepts concerning the balance between pro- and anti-arrhythmic drug action. The conditions atrial fibrillation and heart failure should be kept in mind when reading through this figure. For the sake of clarity, we have assumed in the preparation of this figure that the contribution of the ionic channels to the atrial and the ventricular action potentials is the same (which is not). Also we did not incorporate transmural or interventricular differences in ionic currents responsible for ventricular heterogeneity in APD.

Depending on the mechanism of AF, 3 atrial action potentials can be composed: (a) normal APD in the case of CHF induced AF (upper left panel), (b) slightly shortened APD with early signs of electrical

remodeling, e.g. AF existing less than 48 hours (left middle), and (c) severely shortened atrial APD due to persistent AF with electrical, contractile and structural remodeling (lower left). To the right, 3 ventricular action potentials have been illustrated, again under 3 different conditions: (a) normal ventricular APD (upper right panel), (b) prolonged APD associated with hypertrophy, e.g. hypertension (right middle), and (c) severely prolonged APD as is the case in CHF (lower right). In addition to the electrophysiologic remodeling as outlined here, rate is another important modifier of drug effects. Most class III drugs exhibit reverse use-dependency, i.e. they act stronger during bradycardia but weaker during tachycardia.

Therefore, administration of a class III drug in the acute treatment of AF can give variable results depending on the atrial and ventricular APD as well as the atrial and ventricular rate (in AF the atrial rate is 3 to 4 times higher than normal). When the atrial repolarization is still sufficiently long, AF will be terminated due to sufficient lengthening of APD and despite reversed use-dependency. When the drug is given to tissue which is severely electrically remodeled, the results will be disappointing: no termination of AF because atrial APD is not increased. At the ventricular level, the APD will also increase after the drug and again depending on the existing situation, the end-result may differ between only mild QT-time prolongation, to the initiation of ectopic beats or in the worst scenario TdP.

The above principles also apply during chronic drug treatment. However, during chronic drug treatment one additional factor comes into play: time-dependent changes of the electrophysiologic substrate: for instance, in the course of time patients may develop heart failure due to underlying (non)cardiac disease or due to tachycardia (tachycardiomyopathy). Another important example is reversed electrical remodeling after successful electrical cardioversion of persistent atrial fibrillation (see also above, the different types of recurrences). Presumably, reversed remodeling is associated with a progressive increase in the atrial APD. As a consequence, early after the conversion the atrial anti-arrhythmic efficacy in terms of prophylaxis – even considering marked drug action due to reversed use-dependency at the relative slow atrial rate – is rather limited. However, at the same time, the ventricular pro-arrhythmic potential may be high due to electrophysiologic adaptations associated with left ventricular dysfunction and neurohumoral activation. By contrast, late after cardioversion class III drugs may appear more effective against recurrent AF drugs may appear more effective against recurrent AF and safer in terms of producing TdP.

To maintain a favorable balance between anti- and pro- arrhythmic drug effects is a well known challenge for clinicians for which the above principles may be helpful. These notions may help to avoid futile drug interventions and to target drug treatment to clinical situations where they are most effective.

Future developments

The tachycardia-induced changes in densities and function of channels governing repolarization affect the action of anti- arrhythmic drugs. A potassium channel blocker may be ineffective in the rapid pacing model due to a relative absence of its target channels. By contrast, it may be extremely effective in atrial hypertrophy related AF of short duration. Also, reversal of electrical remodeling after restoration of sinus rhythm may render AF suppressing drugs effective initially but useless later on and vice versa. One consequence might be that after cardioversion of long-lasting AF a time dependent differential anti- arrhythmic approach applies, focused at the stage of (reversed) electrical remodeling. A targeted use of drugs may reduce the time spent on the drug which limits the exposure to pro- arrhythmia and other side effects. A promising example in this respect is the use of amiodarone during 1 month before and after cardioversion (in combination with repeat shocks if necessary) rather than prolonged use for years. To establish optimal use of anti- arrhythmic drugs, i.e. highest efficacy at the cost of only few side effects, the above considerations surely apply. It helps to avoid futile drug applications. In addition, exploration of the various atrial and ventricular electrophysiologic conditions patients experience during the course of AF may help to find specific drug targets and avoid pro- arrhythmic conditions. Indeed, future clinical strategies should take not only static factors into account such as QT time, QT dispersion, renal function and drug dosage, but also dynamic factors such as remodeling, reversed remodeling, use – and reversed use – dependency, time dependent change in renal function, and so on. Concerning new drug development, one way to prevent pro- arrhythmic activity and maintain a strong anti- arrhythmic effect against AF is to develop drugs that are atrium-specific. Alternatively, one may search for drugs safe and effective regardless heart rate and remodeling.

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