Feasibility of selection of antiarrhythmic drug treatment on the basis of arrhythmogenic mechanism - relevance of electrical restitution, wavebreak and rotors

G. André Ng^{1,2,3}

1. Department of Cardiovascular Sciences, University of Leicester, Leicester, UK

2. National Institute for Health Research Leicester Cardiovascular Biomedical Research Unit

3. University Hospitals of Leicester NHS Trust, Glenfield Hospital, Leicester, UK

Professor G. André Ng

Department of Cardiovascular Sciences

University of Leicester, Glenfield Hospital,

Leicester, LE3 9QP, UK

Telephone: +44(0)1162583297

Fax: +44(0)1162875792

E-mail: gan1@le.ac.uk

Abstract

Antiarrhythmic drug therapy has seen significant challenges over the past 3 decades with unexpected results from clinical trials such as CAST, SWORD and more recently PALLAS showing harm in patients whom antiarrhythmic drugs were given based on their intended antiarrhythmic actions and previously demonstrated efficacy. These results question whether the precise mechanism of action of the drugs were understood and highlight the complexity of the situation where there is the combination of multiple actions of the antiarrhythmic drugs on various molecular systems, some of which may be unknown with associated adverse outcome, and their interaction with pre-existing abnormality in disease states in patients treated. In addition, there is no effective drug strategy for complex arrhythmias such as atrial and ventricular fibrillation. Their complex dynamics are not adequately described by the classical mechanisms of automaticity, triggered activity and re-entry. Experimental data showing that flattening of the electrical restitution curve can convert ventricular fibrillation into stable tachycardia and prevent its initiation via wavebreak, and the advancement of computation biology in the describing the behaviour of wavetip and rotors in driving fibrillation have ignited the quest for more detailed understanding of the mechanisms underlying these complex arrhythmias. Their precise ionic basis which could be targeted for drug therapy remain to be fully characterised and tested in appropriate disease models and preparations. This review summarises some of these developments in the context of antiarrhythmic drug therapy consideration.

Keywords: Anti-arrhythmic drug, Fibrillation, Restitution, Rotor

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Abbreviations

AAD = Anitarrhythmic drug

AF = Atrial Fibrillation

APD = Action Potential Duration

APDR = Action Potential Duration Restitution

Ca^{2+} = Calcium

CAST = Cardiac Arrhythmia Suppression Trial

CL = cycle length

CV = conduction velocity

CytoD = Cytochalasin-D

DAM = Diacetyl monoxime

DI = Diastolic Interval

ERP = Effective Refractory Period

HV = His-ventricular

ICaL = L-type Ca^{2+} current

ICD = Implantable Cardioverter Defibrillator

IKr = rapid component of the delayed rectifier potassium current

IKs = slow component of the delayed rectifier potassium current

K^{+} = Potassium

MAP = Monophasic Action Potential

Na^{+} = Sodium

R2I2 = Regional Restitution Instability Index

SCD = Sudden cardiac death

VA = Ventricular arrhythmias

VF = Ventricular Fibrillation

VT = Ventricular Tachycardia

WL = Wave length

1. Introduction

The basic premise of the use of drug in treating diseases takes into consideration the drug's pharmacokinetics, i.e. how the drug is handled in the patient's body, on the one hand and the drug's pharmacodynamics, i.e. how the drug works, on the other. It is therefore imperative that the specific actions of the drug give rise to desirable effects addressing the key mechanisms to target in the underlying disease condition. The journey of drug therapy in treating and preventing arrhythmias over the past several decades has taught us important lessons to highlight that the situation is rather complex in antiarrhythmic drugs (AADs). The Cardiac Arrhythmia Suppression Trial (CAST) (CAST Investigators, 1989; CAST II Investigators, 1992) was a key study which taught one of these important early lessons. Despite effectively suppressing asymptomatic or minimally symptomatic ventricular ectopic beats in patients with prior myocardial infarct, the AADs encainide, flecainide and moracizine resulted in higher mortality than with placebo. As frequent ventricular ectopy and non-sustained ventricular tachycardia (VT) were associated with increased mortality in patients with prior myocardial infarct, the AADs were used to suppress ventricular ectopy in the presumption that these were associated with the key mechanism underlying arrhythmic death in these patients. Not only did the AADs not improve survival in these patients, they actually caused harm. Similar surprises with increased mortality were seen with other AADs, such as d-sotalol in SWORD (Waldo *et al.*, 1996) and more recently dronedarone in PALLAS (Connolly *et al.*, 2011). These results serve serious cautionary lessons which have significantly impeded the development of new AADs. They raised questions which challenge our knowledge about the drug and its actions in targeting the presumed mechanisms in the relevant patients. Was the right drug given for the wrong reason or in the wrong patient or was it the wrong drug from the outset? Especially in the context of life-threatening

ventricular arrhythmias, it is vital that we know about the arrhythmogenic mechanisms at work in the condition and the patient treated, at which the AAD used can specifically target and those not to be made worse by the collateral effects of the drug. This article reviews some of the current knowledge about the mechanisms underlying arrhythmias as potential therapeutic targets and the consideration of AAD selection and future development.

2. Arrhythmia mechanisms

Classic physiological and pharmacological investigations had established the key mechanisms underlying arrhythmias which have been widely recognised and taught in relevant textbooks. These include enhanced automaticity, triggered activity and re-entry. Whilst very helpful in the understanding of many arrhythmias and identifying target for therapy, these classical mechanisms do not adequately describe the situation in complex arrhythmias such as atrial and ventricular fibrillation. The mechanisms underlying the initiation and maintenance of AF are not well characterised and how stable VT degenerates into VF is still poorly understood. This may explain why we still lack an effective drug for AF prophylaxis and for cardioversion of AF and there is still no effective drug that prevents VF and sudden cardiac death.

2.1. Classical mechanisms

The normal functioning of the cardiac myocyte requires electrical impulses to coordinate downstream contraction of the muscle cell via processes involved in excitation-contraction coupling. The electrical impulses normally originate from the sinoatrial node in the right atrium which is the usual pacemaker location, then spreads by conduction pathways either through cell-cell communication via gap junctions or down specialised conduction system like the His-Purkinje fibres to the individual locations. At the myocyte level, these electrical

impulses give rise to the cardiac action potential with distinctive phases, generated by the flow of Na^+ , K^+ and Ca^{2+} ions through transmembrane ion channels (Figure 1A). The local rapid electrical activation (depolarisation) is followed by a more gradual recovery to baseline (repolarisation). The refractory period, during which an activated cardiac cell cannot be excited to generate another action potential, is characteristic of cardiac muscle and is important mechanically to allow proper effective function of the heart as a pump with contraction and relaxation periods in the cardiac cycle. The electrical events and timings are key players in the generation of arrhythmias.

2.1.1. Enhanced / abnormal automaticity

Normal cells at the sinoatrial node exhibit cyclic Phase 4 automaticity whereby a combination of Ca^{2+} , K^+ and the hyperpolarisation-activated nonselective (I_f) currents cause ongoing depolarisation of the membrane potential which once reaching threshold would generate pacemaking action potentials (Figure 1B). Activities of these ion channels at the cell membrane have been classically regarded to be the main drivers for the diastolic depolarisation in pacemaking cells. However, there is good evidence that there is also integrated interaction with intracellular events of local Ca^{2+} releases from ryanodine receptors in a rhythmic fashion (termed Ca^{2+} clock) (Lakatta & DiFrancesco, 2009) which drive membrane channel activity, such as the Na^+ - Ca^{2+} exchanger (NCX), to regulate automaticity. These processes can be enhanced (e.g. with sympathetic activation) under physiological or pathological conditions giving rise to fast heart rates. Ectopic activity can arise from abnormal automaticity in other cardiomyocytes or Purkinje fibres which can give rise to extra beats or even tachycardias.

2.1.2. Triggered activity

This is a second arrhythmogenic mechanism leading to abnormal impulse generation. The abnormal beat is produced subsequent to a previously activated action potential as opposed to occurring spontaneously. The 2 types of triggered activity:- Early After-Depolarisation (EAD) and Delayed After-Depolarisation (DAD) are classified based on the timing whereby EADs occur before phase 3 repolarisation is complete whilst DADs occur after repolarisation is fully complete. EADs are encouraged in situations where the APD is prolonged especially with the blockade of IKr with certain drugs or electrolyte disturbance (e.g. hypokalaemia and hypomagnesaemia) and with slow heart rates. DADs are usually the result of Ca^{2+} overload under pathological conditions or with drugs and catecholamines.

2.1.3. Re-entry

This is the mechanism underlying a majority of clinically significant arrhythmias ranging from benign atrioventricular nodal re-entrant tachycardia to life-threatening scar-related ventricular tachycardia. There are three known criteria for re-entry to occur:

1. two or more parallel pathways of conduction are present and connected with each other
2. unidirectional conduction block in one pathway
3. the conduction time around the circuit must be longer than the ERP of any cells within the circuit.

Classical re-entry was demonstrated in rings of tissues by Mines (Mines, 1913) and Garrey (Garrey, 1914) in the turn of the 20th century where an anatomical separation between the conduction paths exist and around which the re-entrant waves circle once formed. The size of the waves, i.e. wave length (WL), is described by the product of the refractory period (RP) of the tissue and conduction velocity (CV). The equation is therefore: $\text{WL} = \text{RP} \times \text{CV}$. This

relationship is helpful especially for therapy consideration as any condition that increases the size of the WL might make it too big for the circuit in which it is circling and hence conduction stops or that it grows to hit anatomical obstacle that causes conduction block with the same resultant effect of arrhythmia termination.

2.2. Arrhythmogenic mechanisms underlying cardiac fibrillation

Atrial and ventricular fibrillation manifest as irregular electrical activity in the respective cardiac chambers which appears random. Efforts to explore their possible mechanisms have been reviewed in reasonable detail (Jalife, 2000; Nattel, 2002). A brief summary of the original discoveries that contribute to our current understanding will be provided below.

2.2.1. From multiple wavelet theory, non-uniform refractoriness to wavebreak

Gordon Moe was first to suggest that the mechanism of fibrillation was different to that for tachycardia and proposed the “multiple wavelet” hypothesis of atrial fibrillation (Moe, 1962). The hypothesis was based on the presence of spatial and temporal distribution of electrical properties of the atrial tissue and gained enormous popularity with the consolidation of the concept with the emergence of the first computer model of cardiac fibrillation (Moe *et al.*, 1964). Using a 2-dimensional cardiac tissue model of cellular automata with coupled excitable components, it was shown that introduction of random heterogeneity in refractory periods can lead to cardiac waves spontaneously breaking into wavelets. Direct experimental evidence took another 20 years to emerge when Allessie (Allessie *et al.*, 1985), using multielectrode plaques to map the surface of the fibrillating canine atrium, showed multiple wavelets to propagate in a similar manner to the predicted multiple wavelets meandering in apparently random patterns. This has also been shown in the ventricles (Weiss *et al.*, 2000a). The importance of pre-existing electrical heterogeneity in refractoriness forms the basis for the generation of fibrillation according to the multiple

wavelet theory. The pioneering work of Han and Moe (Han & Moe, 1964) demonstrated that dispersion of recovery was increased by conditions that predispose to VF, e.g. sympathetic stimulation and cardiac glycoside toxicity; and that the increased dispersion was associated with increased VF inducibility. Around the same time, Krinsky (Krinsky VI, 1966) provided additional mathematical support for the importance of inhomogeneous refractoriness in fibrillation and added insight into the concept of critical mass. Elegant experiments by Kuo et al. (Kuo *et al.*, 1983) further detailed the initiation of re-entrant ventricular arrhythmias with a critical level of dispersion of monophasic action potential (MAP) duration. It is logical to extend the proposal to the importance of pre-existing heterogeneity in refractoriness to sustain VF in diseased hearts. Neighbouring cardiac regions with different refractory periods can therefore be inactive in one region and active in the other providing an ideal medium of re-entry which can be set up by a suitable cardiac wave. The existing electrical activity can exploit the underlying heterogeneity further to perpetuate further re-entry and hence produce multiple wavelets. The re-entry envisaged here is different from classical re-entry as an anatomical barrier or separation between different conduction paths is not present. The important realisation that re-entry can exist without an anatomical obstacle was provided by the “leading circle” hypothesis proposed by Allesie (Allesie *et al.*, 1977). This type of functional re-entry occurs with centripetal excitation from a circulating wavefront which makes the central core refractory, around which the re-entrant wave encircles. The association of these functional re-entrant “spiral waves” with fibrillation had been proposed previously in Krinsky’s work.

In exploring the mechanistic relationship between spiral waves and fibrillation, mathematical modelling investigations using more realistic ionic models of cardiac tissue demonstrated that fibrillation can occur in the absence of pre-existing heterogeneity in

refractoriness (Panfilov & Holden, 1990). In a homogeneous sheet of cardiac tissue, it was shown that a stable spiral wave can, after a few rotations, “break” around the core and produce a daughter wave which can again break to give more wavelets. This provides a different view to the original multiple wavelet hypothesis proposed by Moe where the re-entry waves arise from heterogeneities in refractoriness. Here, spiral breakup of the rotating waves occurs without pre-existing non-uniformity of refractoriness. An alternative explanation is required for the conceptualisation of wavebreak.

From a clinical perspective, pioneering work by Michel Haissaguerre demonstrated that atrial ectopy generated by electrical activity or “firing” from the pulmonary veins precede the initiation of AF (Haissaguerre *et al.*, 1998) and catheter ablation targeted at the pulmonary veins has become established therapy especially in patients with paroxysmal AF (Haissaguerre *et al.*, 2000). Subsequently, Haissaguerre also proposed that electrical activity from the His-Purkinje system can also lead to VF initiation in a similar manner to AF in patients with idiopathic VF (Haissaguerre *et al.*, 2002). Whilst ectopic activity can be explained by mechanisms underlying impulse generation, and hence issues of enhanced automaticity and triggered activity according to classical mechanisms, additional understanding is required as to how ectopy and in some cases repetitive activity leads to the generation of the seemingly irregular fibrillation. Does wavebreak play a part and if so is this the underlying mechanism that describes how stable VT “degenerates” into VF (Weiss *et al.*, 2000b)? Instability in the dynamics of myocardial repolarisation is believed to contribute to wavebreak and this will be explored below in the studies of electrical restitution.

2.2.2. Action Potential Duration Restitution

It is a normal intrinsic property of the APD of myocardium to vary according to the activation rate. At slow heart rates, APD is long whilst at faster heart rates, APD shortens

(Figure 2A & B). This property is termed APD restitution (APDR). This is important for the mechanical function of the heart where at faster heart rates, the cardiac cycle is shortened to allow brisker contraction and relaxation for efficient pump function of the heart. APDR is also not a novel concept but is embedded in the conceptual need for rate correction of the QT interval (surrogate of ventricular APD) on ECG with the acknowledgement of the relationship between QT and heart rate (Ahnve, 1985). The APD of a beat is dependent on the preceding diastolic interval (DI) and APDR describes the situation whereby a shortening of the DI leads to a shortening of the following APD. The relationship can be described by plotting APD against DI which usually assumes an exponential curve (Figure 2C). At slow heart rates, i.e. long DI, changes in DI lead to relative little change in APD with a flat APD-DI relationship. During restitution, APD shortens as DI decreases. At the steep part of the APDR curve, small changes in DI would lead to large changes in APD. The importance of the dynamics of the relationship between APD and DI was appreciated as early as 1968 when Nolasco and Dahlen (Nolasco & Dahlen, 1968) demonstrated, in frog ventricular muscle strips, that APDR slope increased and transient alternation in APD lasted longer when stimulus frequency was increased. At a driving rate where APDR slope was +1, persistent alternans occurred. This was interpreted graphically in the light of a feedback mechanism, illustrated in Figure 3. If the APDR relationship is shallow with a slope < 1 , a brief perturbation e.g. as a result of an ectopic beat will lead to a shorter DI, resulting in a shorter APD. Assuming that the heart rate is maintained constant i.e. cycle length (CL, the sum of APD and DI) is constant and this relationship can be plotted as a straight line with the formula $APD = -DI + CL$ and a slope of -1. The following DI will be longer, which makes the next APD less short as a result of the flat APDR curve and a stabilisation of the APD oscillations (Figure 3A). On the other hand, if the APDR slope is > 1 , a shortening in DI, will lead to more pronounced APD shortening, with amplification of effects on subsequent DI

prolongation and setting up of APD alternans (Figure 3B). Thus the negative feedback if APDR slope is < 1 and positive feedback if APDR slope is > 1 serve to dampen or exaggerate oscillations and alternans respectively.

The demonstration that APD alternans can lead to breakup of spiral waves into a fibrillatory state was first provided in 1993 by Karma (Karma, 1993) in a two dimensional tissue simulation without spatial inhomogeneities. The role that APDR slope plays in the generation of fibrillation through wave break was verified by biological data that came soon after (Riccio *et al.*, 1999)(Garfinkel *et al.*, 2000). It was first shown in arterially perfused canine ventricular endocardial preparations that drugs that reduce the APDR slope (diacetyl monoxime (DAM) [15mM] and verapamil [2 μ M]) prevented the induction of VF whilst the drug procainamide [10 μ g/mL] which does not reduce APDR slope did not prevent VF induction (Riccio *et al.*, 1999). More spectacularly, DAM and verapamil converted VF into stable VT whereas procainamide did not lead to spatiotemporal organisation of VF. Similar findings were shown with bretylium in perfused swine right ventricular preparations, in which there was flattening of APDR curve, prevention of wavebreak and thus fibrillation induction and also converted VF into a periodic rhythm (Garfinkel *et al.*, 2000). These studies provide strong experimental support for the “restitution hypothesis” and opened up lines of investigations both to explore the importance of APDR in mechanisms underlying arrhythmogenic conditions and also the possibility of manipulating APDR to reduce wavebreak and prevent or treat fibrillation.

2.2.2.1. Ionic basis of APDR

The situation during APD restitution whereby a small reduction in DI causes greater APD shortening, occurring either with a premature beat or faster heart rate, means the ensuing beat occurs with a shorter APD either with less inward current or more outward current

than the previous beat. As the myocardial action potential is largely composed of movements of Na^+ , Ca^{2+} and K^+ ions, a simplified three-component model had been proposed to denote the ion currents at work during the various portions of the APDR curve (Franz, 2003). As acknowledged by the author, this was an extremely simplified view considering the complexity of the various processes occurring during the cardiac cycle and with perturbations. It was proposed that as the upstroke of a very premature beat is usually reduced, the steepest part of the APDR curve would be largely due to the incomplete recovery from inactivation of the Na channel. At longer DI, the activation and feedback (from sarcoplasmic reticulum Ca^{2+} release and reuptake) would engage effects from the ICaL followed by IKr and IKs which control the later part of repolarisation and hence dynamics at longer DI. Early work had shown that both the incomplete reactivation of ICaL at short coupling intervals with the resulting reduction in ICaL (Gettes & Reuter, 1974) and incomplete deactivation of IK with the consequent additional IK (Hauswirth *et al.*, 1972) could explain APD shortening with premature beats during APDR. However, there is also evidence that other currents such as the Na^+ - Ca^{2+} exchanger also contribute significantly in APDR (Janvier *et al.*, 1997) with the support that any time-dependent current that contributes to the action potential is likely to affect the time course of electrical restitution. Hence, whilst the understanding of the ionic basis of arrhythmogenesis from APDR mechanisms is important obviously for the development of therapeutic approaches, the dynamicity of the processes occurring during the action potential and cardiac cycle at larger and the interactions with pre-existing heterogeneities in pathological states pose a substantial challenge.

2.2.2.2. Cardiac disease, autonomic modulation and regional APDR heterogeneity

Cardiac diseases such as heart failure and myocardial infarction are associated with increased mortality and sudden death due to malignant ventricular arrhythmias. Altered autonomic tone has been shown to be a strong prognostic marker in these patients (La Rovere *et al.*, 1998; Nolan *et al.*, 1998). In an attempt to understand the association between autonomic activity and arrhythmogenesis, our group has examined the role that APDR plays in the autonomic modulation of VF initiation using a unique innervated isolated heart preparation (Ng *et al.*, 2001). In this *ex vivo* preparation, we showed that sympathetic nerve stimulation increased the APDR slope, promoted APD alternans and lowered the threshold current required to induce VF, i.e. increased VF susceptibility (Ng *et al.*, 2007). Vagus nerve stimulation had opposite effects – reduced APDR slope, APD alternans and VF inducibility. The increase in APDR slope has also been shown in human patients using adrenergic agonists isoprenaline or adrenaline (Taggart *et al.*, 2003). The first clinical data that APDR dynamics are associated with clinically relevant arrhythmia events and sudden death came from the translation of our preclinical findings to clinical studies in patients at risk of sudden cardiac death. Whilst the restitution hypothesis does not require spatial heterogeneity in electrical properties to generate wave break and fibrillation but is based on the temporal dynamic instability of APDR, our studies have identified heterogeneous behaviour of APDR in the beating heart (Ng *et al.*, 2009). Sympathetic stimulation revealed the differences in APDR characteristics between the base and apex of the left ventricle due to increased sympathetic innervation and also increased abundance of the adrenergically sensitive IKs channels at the base compared to the apex. It should be noted that these regional differences demonstrated by sympathetic nerve stimulation were not revealed by classical sympathomimetic pharmacological manoeuvres with isoprenaline in the same preparations (Mantravadi *et al.*, 2007).

Referring back to Figure 3B, the final beat landed on the refractory period of the APD and therefore would not cause depolarisation but result in conduction block. It could be envisaged that a neighbouring cell with a less steep APDR curve would have a shorter APD at this instant and therefore could conduct, thereby generating an ideal scenario for re-entry. This was elegantly demonstrated in a 2D simulation of cardiac ventricular tissue with regional differences in APDR not only setting up re-entry but also resulting in wavebreak (Clayton & Taggart, 2005). However, in this case, re-entry and wavebreak generation was not dependent of the steepness of the APDR curve. Similar challenges to the “restitution hypothesis” premise have been proposed where the association between APDR slope and arrhythmogenesis appeared to be uncoupled (Banville & Gray, 2002) in optical mapping experiments in isolated rabbit hearts using voltage-sensitive dyes and the mechanical uncouplers DAM and Cytochalasin-D (CytoD) (which are required to inhibit motion and remove resultant artefact). On one hand, arrhythmia could still be induced with DAM despite a flatter APDR slope, albeit with shorter APD and the arrhythmia stabilised into VT. On the other, CytoD steepened APDR slope but arrhythmia was not inducible. This may be due to effects on conduction and hence restitution of conduction velocity (reduction of conduction velocity with short DI) and / or the fact that APD was prolonged with CytoD. One important finding in this study is that mechanical uncouplers can cause significant electrophysiological effects which have important implications in the interpretation of arrhythmia mechanisms in optical mapping studies, an aspect which will be discussed further in later sections.

Hence, the spatial heterogeneity in APDR characteristics whether pre-existing or encouraged by extrastimuli, could be operating separate from steep APDR to give rise to wavebreak and fibrillation. Our group extended these insights into a clinical retrospective

study and measured APDR curves obtained using a single ventricular extrastimulus programmed stimulation protocol in patients with ischaemic cardiomyopathy assessed for arrhythmic risk (Nicolson *et al.*, 2012). Using digital ECG data with QT and TQ intervals as surrogates for APD and DI respectively, APDR curves were plotted and APDR heterogeneity across the 12 leads and over time across the stimulation protocol was quantitated as Regional Restitution Instability Index (R2I2). It was found in this pilot study that R2I2 predicted ventricular arrhythmia or death as an independent marker, the results of which were replicated in a separate validation group. We applied the predefined cutoff ($R2I2 \geq 1.03$) to a new prospective group of patients and showed this marker of APDR heterogeneity was similarly raised in patients with ventricular arrhythmias (VA) or SCD as was the peak ECG restitution slope (PERS) (Nicolson *et al.*, 2014). In addition, patients who were positive for both $R2I2 (\geq 1.03)$ and $PERS (\geq 1.21)$ had a relative risk of VA/SCD 21.6 times that of those negative for both. These are the first data to show that APDR slope and heterogeneity are associated with clinical ventricular arrhythmia and sudden death in cardiac patients and could be strong prognostic markers. This gives reason for enthusiasm to develop anti-arrhythmic strategies which may reduce the slope of APDR curve and / or reduce the heterogeneity of APDR in the heart.

2.2.3. Rotor

Use of the term “rotor” has gained a lot of popularity of late in discussing the mechanisms underlying cardiac fibrillation (Pandit & Jalife, 2013). This is partly driven in the clinical electrophysiology arena with catheter mapping and ablation studies suggesting that “rotor” sites may represent driver locations for fibrillation and hence targets for successful ablation and elimination of fibrillation (Schricker *et al.*, 2014). What is a “rotor”? The term takes its origin from nomenclature in computational biology studies of wave propagation in excitable

media. Properties of stable rotating waves, referred to as rotors, were originally described using reaction-diffusion equations (Winfree, 1978). Different investigators have contributed to the understanding of the role of rotors in cardiac fibrillation [reviewed in (Winfree, 1998)]. Put simply, a rotor is a functional re-entrant circuit, similar to that described with the leading circle theory by Allesie (Allesie *et al.*, 1977), with re-entry occurring in the absence of an anatomical obstacle. However, the main distinctive feature is that the core is not made refractory by centripetal activation but is excitable. Winfree (Winfree, 1989) described it as a rotating wave in a uniform excitable media without holes and further elaborated it to be an area where the wavetip turns around the pivot (phase singularity) while the attached wavefront wraps into an outgoing “spiral wave” around it. The generation of rotors and spiral waves has been elegantly presented in simulation studies illustrating the phenomenon of “vortex shedding”, which is similar to the generation of eddies or turbulence when flowing water hits rocks in the river bed (Cabo *et al.*, 1996). It was also highlighted that the curvature of the wavefront is important in determining whether the wave wraps around and remain attached to the obstacle or the vortex is detached to generate re-entry, when the wavefront curvature is less than the critical curvature for detachment. Vortex shedding is also important in generating wavebreak from a rotor, which results in fibrillatory conduction. The interface between the depolarised wavetip (source) and unexcited tissue (sink) generated by the curvature of the wave where there is source-sink mismatch is responsible for both rotor initiation and perpetuation.

2.2.3.1. Mother rotor vs. multiple wavelet hypothesis

The revived interests in applying nonlinear mathematical approaches to studying pathophysiology in the 1980s had raised questions as to whether the seemingly random and ‘chaotic’ (used in the colloquial sense) rhythm could represent a deterministic (as opposed

to stochastic) process that can be analysed and described with the mathematics of chaos theory (Goldberger *et al.*, 1986)(Kaplan & Cohen, 1990). Using spectral techniques, it was found that the power spectrum of the fibrillation signals contain distinctive spikes of dominant frequency suggesting that there could be an “organised” source underlying this chaotic rhythm. Further work in the 1990s provided evidence that the electrical activity during VF is not random but exhibits deterministic behaviour (Witkowski *et al.*, 1995) which can be analysed using chaos theory (Garfinkel *et al.*, 1997). Experiments using voltage-sensitive fluorescence dyes have revealed spatiotemporal organisation of electrical activity in VF (Witkowski *et al.*, 1998)(Gray *et al.*, 1998). High frequency periodic sources have also been demonstrated during VF suggesting that there are ongoing stable electrical sources that are responsible for its maintenance (Chen *et al.*, 2000). This gave rise to the focal source or ‘mother rotor’ hypothesis with the proposed scenario whereby a dominant ‘mother’ rotor drives the arrhythmia with wavebreaks leading to multiple ‘daughter’ wavelets. Whilst the evidence provided for this is compelling, it should be noted that most if not all of the data collected with optical mapping were based on the use of mechanical uncouplers which are required to eliminate motion artefact and these have been shown in many previous (Banville & Gray, 2002)(Kettlewell *et al.*, 2004) and more recent studies (Brack *et al.*, 2013) to have significant effect on cardiac electrophysiology in both activation and repolarisation with the genuine possibility of affecting VF dynamics and hence the interpretation of results. In some early uncouplers, it was either impossible to induce VF or that VF converted to stable VT (Banville & Gray, 2002).

The ‘mother rotor’ hypothesis (Jalife *et al.*, 2002) is in contrast to the classical ‘multiple wavelet’ hypothesis and more recent evidence in support of the latter found that the frequency clusters during VF had a short life span, were dynamically changing and could be

modified by pharmacological interventions which suggest that VF was maintained by dynamically changing multiple wavelets (Choi *et al.*, 2002). Also, others (Valderrábano *et al.*, 2002) have failed to find evidence of stationary dominant frequency domains. This had led to heated debates between supporters of the 2 camps (Choi *et al.*, 2001)(Berenfeld *et al.*, 2001). Whilst the discrepancy between the experimental evidence provided in support of the 2 hypotheses could be due to properties of the optical equipment used, with spatial and/or temporal resolution differences and those of species of hearts studied, subsequent experimental data proposed that the different dynamic behaviour could be explained by the different types of VF studied. Using the mechanical uncoupler, methoxyverapamil (D600) in increasing concentrations, the UCLA group showed in rabbit hearts that 'fast VF' (with higher dominant frequency) was converted first to VT and then 'slow VF' (Wu *et al.*, 2002). Wandering wavelets were seen in 'fast VF' at the initial low D600 concentration where APDR slope was steep and conduction time restitution was flat. In contrast, at high D600 concentrations, APDR slope was flat but conduction time restitution was steep where stable VT converted to slow VF and spatiotemporal periodicity was seen. This attempt to ratify the differences between the 'mother rotor' and 'multiple wavelet' hypothesis has highlighted the importance of both excitability and APDR in VF dynamics. Under normal excitability, where there is steep APDR but flat CV restitution, VF activation appears faster consistent with a multiple wavelet mechanism. With low excitability, where APDR is flat and CV restitution is steep, VF activation appears slower and significant spatiotemporal organisation exists with the appearance of a focal and relatively stable source or 'mother rotor' driving VF. This also helps to add context to the original description of the 4 distinct stages of VF by Wiggers from cinematographic studies (Wiggers, 1940). The first (undulatory) *tachysystolic* stage is short (<2s) is followed by the second *convulsive incoordination* stage lasting 15 – 40s where multiple wavelets have been shown in

subsequent studies (Lee *et al.*, 1996) with meandering cores of re-entrant waves which would correspond to the proposed 'fast VF' characteristics. The third Wiggers' stage of VF is termed *tremulous incoordination* which lasts 2-3 min followed by the fourth *atonic fibrillation* stage during which 'increasing anoxia causes depression of contractile force, slows conduction and eventually leads to regional blocks and complete failure of contractility' (Wiggers, 1940). The latter stages would fit with the proposed 'slow VF' characteristics.

2.2.3.2. Ionic basis for rotors

The notion of rotors driving fibrillation stems from the description of spatio-temporal organisation in its kinetics and the finding of frequency signatures in the power spectrum. Hence explorations of the ionic basis for rotors are based on ion channels which might affect their dominant frequencies. Phase analysis allows points, called singularities, where phase contours converge to be analysed. The phase singularities represent centres of vortex-like rotating activity, such as rotors, acting as "hinges" on which electrical activity turns and can be mathematically quantitated. Outward currents such as IK1 (Warren *et al.*, 2003) and IKACH (Sarmast *et al.*, 2003) have been implicated to be important drivers in VF and AF according to their predilection in LV>RV and LA>RA chamber-specific gradients respectively and barium chloride which blocks IK1 causing VF termination and reduced rotor frequency and phase singularity density. Inward currents were also shown to be important with verapamil (which reduces I_{CaL}) reducing dominant frequency of VF, increasing core meander and converting VF to VT whilst tetrodotoxin (sodium channel blocker) also reduces dominant frequency of VF and increases core area with both drugs reducing phase singularity densities. Other ion channels are likely to be involved (Pandit & Jalife, 2013) in the maintenance of rotor, their initiation and termination. Modelling studies have helped in

probing such mechanisms but have also highlighted the complexity especially taking into consideration wavetip kinetics, fibrillatory conduction and other properties such as postrepolarisation refractoriness (Munoz *et al.*, 2007). Interaction with remodelling in pathological states also requires further understanding from which to develop specific therapeutic strategy.

3. AADs and their classification

The organisation of AAD into groups with similar actions originated from work by Vaughan Williams and Singh in the 1970s (Vaughan Williams, 1970)(Singh & Vaughan Williams, 1970a)(Singh & Vaughan Williams, 1970b). It was based on clinical observations, grouping together such agents (of which there were only a handful then) according to their predominant electrophysiological effects. At first, quinidine, disopyramide and procainamide were all found to prolong His-ventricular (HV) and QT intervals during sinus rhythm as well as widen the QRS complex, actions that were designated as class Ia. Lignocaine, mexiletine and tocainide did not produce any of these effects (but shortened QT interval) and this action was classed as Ib. The drugs flecainide and encainide caused QRS widening and HV prolongation with little effect on QT, and were put into a further class termed Ic. These changes were found to correspond to actions on the upstroke with effects on the fast Na current and also repolarisation phases of the action potential (Figure 4). Also, the dissociation kinetics following Na channel block are distinctive between the three groups of class I drugs. Class Ic drugs dissociate very slowly and incompletely with potential for cumulative block on successive beats. Class Ib drugs unbind rapidly with little residual Na channel block between beats and dissociation kinetics for class Ia drugs are intermediate between Ib and Ic (Harrison, 1986). Other drugs were found to have antiarrhythmic efficacy but did not have a prominent fast sodium current effect and classes II, III, IV and V emerged

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with subsequent modification of the original classification (Vaughan Williams, 1984) and new drugs being made available over time (Table 1). However, it is by no means perfect as AAD research [review in (Walker, 2006)] into the nuances of the mechanisms of actions of individual AADs identified important differences in drugs within the same class and also showed that a particular AAD can have actions belonging to different drug classes. The surprise results of the CAST study (CAST Investigators, 1989; CAST II Investigators, 1992) also shocked the clinical arrhythmia community with the energised search for more accurate knowledge and description of AAD actions. It was from that basis that an alternative ‘Sicilian Gambit’ approach to AAD classification was proposed in 1991 (Rosen *et al.*, 1991) following a meeting of basic and clinical arrhythmia investigators in Sicily. The new schema focussed on tentative arrhythmogenic mechanisms at the molecular, cellular and organ levels with the introduction of the “vulnerable parameter” concept to aim at the most appropriate targets for therapy in specific clinical arrhythmias. It contained an inventory with a multifarious log of AAD actions on various channels, receptors and pumps but it was generally regarded that whilst it is helpful for furthering AAD and arrhythmia research, its application for guiding clinical AAD selection was limited due to its complexity (Harrison, 1992; Garratt & Griffith, 1996). The original Vaughan Williams classification of AAD has survived the test of time and is still widely used in the consideration of ADD to treat or prevent arrhythmias.

4. AAD actions to target arrhythmogenic mechanisms

4.1. AAD actions to target impulse generation and propagation

The starting point in the use of AADs to treat arrhythmias usually involves the consideration of whether to target impulse generation, propagation or both. Enhanced automaticity and/or triggered activity which can cause ectopic and focal tachycardias would be initially

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targeted with reducing impulse generation in mind, to try and reduce ectopic firing. Beta-blockers (Class II AADs) are usually used and sometimes Ca^{2+} channel blockers may be effective (Class IV AADs) if there is a triggered activity mechanism driven by Ca^{2+} overload. In terms of propagation modification in re-entrant tachycardia involving tissues with decremental conduction properties (like the atrioventricular node), Class IV AADs are usually used to slow conduction in an attempt to prevent re-entry. They may also be considered in conditions such as idiopathic left ventricular tachycardia (or fascicular tachycardia) where the arrhythmogenic mechanism is one of micro-reentry at the left ventricular Purkinje fascicles. However, AADs are not 100% effective and breakthrough arrhythmias can still occur despite adequate dosage and systemic side effects from drugs also pose challenge. With the advent and successful development of interventional electrophysiology techniques, catheter ablation has become first-line treatment of choice for many of the more “straightforward” arrhythmias (Scheinman *et al.*, 2003). In some pressing scenarios such as pre-excited AF where there is AF conducted with a fast ventricular response due to accessory pathway conduction with short refractory period which could lead to life-threatening VF, catheter ablation should be carried out as a matter of urgency rather than persevering with AAD such as flecainide (Class Ic) to try and prolong accessory pathway refractory period (Ng & Rankin, 1999) with incomplete protection. Another interventional electrophysiology development which has changed the attitude and approach to AAD treatment came in the form of the implantable cardioverter defibrillator (ICD). Since the demonstration that ICDs prevent sudden cardiac death in both secondary and primary prevention trials and that they improved survival compared with AADs, their increasing clinical use with time is now firmly embedded in contemporary guidelines (Zipes *et al.*, 2015). The previous stalwart effort of serial drug testing to arrive at a particular AAD with a particular dose which either renders malignant VT non-inducible or

haemodynamically stable in the pre-ICD era (Reiter *et al.*, 1995) and the clinical thinking that came with it had been almost completely transformed. Patients deemed high risk of sudden death would be implanted with the ICD first usually with no initial consideration of AAD for fear of side effects outweighing benefits. The OPTIC trial demonstrated that the combination of betablocker and amiodarone was effective in preventing ICD shocks from ventricular arrhythmias and was more effective than sotalol which was more effective than a betablocker but there was an increased risk of drug-related adverse effects (Connolly *et al.*, 2006). Whilst ICDs do not represent a curative but palliative therapy, AADs have been pushed further into the background in the consideration in patients at risk of malignant ventricular arrhythmias, being prescribed more for the need of reducing ICD shocks from recurrent arrhythmias than being instituted as pre-emptive treatment. The issues with known adverse effects as shown in the OPTIC trial and the aftershocks still rumbling in the background from the early CAST, SWORD and more recent PALLAS trials from previously unknown adverse effects from AADs serve to take an attitude of “keeping the beast behind cage”. This has hampered AAD development over the past 3 decades. Is it because we need better understanding of complex arrhythmias such as AF and VF and the effects of AADs on their mechanisms?

4.2. AAD actions to target fibrillation mechanisms?

Historically, the actions of AAD on arrhythmogenic mechanisms of fibrillation had been largely conceptualised on the basis of the “multiple wavelet hypothesis” and the concept of “critical mass”. Fibrillation is considered to be maintained only if there is a large enough mass of tissue for the small enough wavelets to wander around. Either if the tissue is too small or the wavelets too big, they will either hit anatomical barrier or extinguish each other, with the previous proposal of critical number of waves that need to exist to

perpetuate fibrillation. This has led to the application of the concept of wavelength (i.e. product of refractory period and conduction velocity, discussed above) and the potential effects of AADs on its components in their effects on fibrillation. Whilst drugs that prolong refractoriness, such as Class Ia and III drugs, would increase WL which may be its chief antiarrhythmic mechanism, others such as Class Ic drugs may also be antiarrhythmic without effects on WL, and the effects on conduction of the latter may actually be reducing WL and perpetuating fibrillation. Elegant studies from Allesie's group introduced and validated the concept of "excitable gap" during AF in the goat model and showed that flecainide can reduce WL (by reducing CV with little effects on RP) but increase pathlength (AF cycle length) with increase in excitable gap (Wijffels *et al.*, 2000). The importance of preferential conduction delay at the pivot points of turning wavelets was also highlighted. In the light of more recent knowledge of APDR, wavebreak and rotor dynamics being important fibrillation mechanisms, what are the AAD options in targeting these?

4.2.1. APDR as AAD target

The initial observations that drugs and other agents like verapamil, bretylium and DAM (Riccio *et al.*, 1999)(Garfinkel *et al.*, 2000) can convert VF into stable VT by flattening the slope of the APDR curve provided strong support for the investigations into manipulating this electrophysiological parameter to develop AADs that target the arrhythmogenic mechanism of fibrillation via wavebreak. As discussed above, the ionic basis of APDR is complex and would interact significantly with pre-existing heterogeneities in disease and altered autonomic states. Nonetheless, many other studies (Omichi *et al.*, 2002; Pak *et al.*, 2006; Jin *et al.*, 2008; Ashino *et al.*, 2011; Morita *et al.*, 2011; Osaka *et al.*, 2011; Osadchii, 2014; Pezhouman *et al.*, 2014) (Table 2) have supported the possibility of favourably altering atrial or ventricular fibrillation kinetics or susceptibility by reduction of the slope of APDR

curve. Amiodarone is the most potential antifibrillatory drug widely used in the clinical setting (Orfano, 2000). It has always been appreciated that the Class III actions of amiodarone prolongs refractoriness and QT significantly and yet there is very little risk of proarrhythmia with torsade de pointes. Whilst reduction of APD dispersion despite APD prolongation may be relevant, the evidence that amiodarone reduces APDR slope in both animal and human studies (Omichi *et al.*, 2002; Osaka *et al.*, 2011) highlight that its actions on electrical restitution (including CV restitution) may play an important role in its antiarrhythmic mechanism.

As mentioned above, spatial and temporal APDR heterogeneity could promote instability and arrhythmogenesis, and have promise as a clinical prognostic marker for arrhythmic risk (Nicolson *et al.*, 2014). Drug studies have also shown that reduction in the dispersion of APDR by ibutilide reduced defibrillation threshold in open chest canine hearts (JIN *et al.*, 2012). Hence, drugs which are aimed at both reducing the APDR slope and the dispersion of APDR curves could pose to be potential antifibrillatory agents. We have shown in the innervated isolated heart preparation that vagus nerve stimulation increases the VF threshold (i.e. making it more difficult to induce VF) by flattening the APDR curve, a mechanism which is abolished by inhibiting nitric oxide synthase activity (Brack *et al.*, 2001). We have also shown that the antifibrillatory effects of vagus nerve stimulation on the ventricle was dependent on release of NO from neuronal NO synthase in a manner which is independent of muscarinic activation, whereby supporting a separate vagal-nitrergic pathway in the heart (Brack *et al.*, 2011). Whilst the ion channels involved in the effect on APDR and protective effect against VF have not been fully characterised, it is very possible that the vagus-NO downstream pathway can be explored as an antiarrhythmic strategy.

Whilst slope of the APDR curve is important, the situation appears complex for some inherited arrhythmias and, indeed, for distinct mutations to single ion channel genes. For example, in the short QT syndrome, the first identified KCNJ2 mutant (D172N-Kir2.1) was reported through simulations to increase slope of the APDR curve (Priori *et al.*, 2005; Adeniran *et al.*, 2012), whilst in familial AF with the V93I-Kir2.1 mutation, the APDR curve is flattened (Kharche *et al.*, 2008). Both spatial and temporal vulnerability and their interactions are important and enhanced risk can occur despite flattening of APDR. Further insight can be obtained from studies in conditions with specific mutations such as these channelopathies.

4.2.2. Rotor dynamics as AAD target

Maintenance of high frequency organised electrical sources in the form of rotors have also been shown to drive fibrillation as detailed above with its accompanying complex dynamics. Studies have explored the effects of pharmacological agents on rotor dynamics, phase singularity densities and core areas implicating the importance of certain ion channels (Mandapati *et al.*, 1998; Samie *et al.*, 2000; Noujaim *et al.*, 2011) (Table 2). The precise mechanisms of rotor formation or kinetics, with the requirements of source-sink mismatch and how these could be modified by AADs for development as antifibrillatory targets require more investigation.

4.2.3. Disease state considerations

4.2.3.1. Ion channel remodelling

As mentioned above, pre-existing heterogeneities in disease states can interact with APDR dynamics and the effects of AADs may be modified because of structural factors and dynamic factors such as altered ion channel remodelling in disease. A consistent ionic phenotype in heart failure and cardiac hypertrophy is the downregulation of outward

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currents with a result increase in repolarisation time and refractoriness (Beuckelmann *et al.*, 1993). It is therefore important to explore fibrillation dynamics in the light of these changes and in relevant disease models and preparations (Hsieh *et al.*, 2013).

4.2.3.2. Autonomic states

Autonomic state is abnormal in many cardiac diseases including heart failure and post-myocardial infarct. Sympathetic overactivity and parasympathetic withdrawal are hallmarks with measures of autonomic tone shown to be strong prognostic markers (La Rovere *et al.*, 1998; Nolan *et al.*, 1998). Adrenergic stimulation has been shown to be pro-arrhythmic by increasing dispersion of refractoriness in the classical Han and Moe experiments (Han & Moe, 1964) and also via steepening of the APDR curve in more recent data (Taggart *et al.*, 2003; Ng *et al.*, 2007). It is known that a heightened sympathetic state can interact with AADs and reduce their efficacy (Sager, 1998). Betablockers have been shown to have an effect in reducing sudden cardiac death in heart failure patients (Al-Gobari *et al.*, 2013). This may be due to its antiadrenergic effect by inhibiting its arrhythmogenic potential which may be mediated via flattening of the APDR curve (Hao *et al.*, 2004) or there may be direct effect of betablockers on the APDR curve as shown in isolated hearts in the absence of tonic adrenergic activity (Pak *et al.*, 2003).

4.2.3.3. Specific channelopathies and syndromes

Class Ib drugs such as mexiletine block Na⁺ channels and shorten APD / refractoriness. These have been shown to normalise the QT interval in LQT3 patients, which is the inherited long QT syndrome as a result of gain of function in the sodium channel (from mutations of the SCN5A gene), and reduce arrhythmias although not reducing mortality (Ruan *et al.*, 2008). Mexiletine did not have the same effects on other LQT patients (LQT2) where QT prolongation was due to another mechanism. This further complicates the issue in that not

only the presumed electrophysiological mechanism needs to be considered in terms of selection of drug to target but also the underlying ion channel effects and in inherited conditions the particular mutation-specific characteristics to consider. Increased recognition of rare arrhythmogenic syndromes and their response to AADs, e.g. quinidine in reducing recurrent VF episodes in patients with idiopathic VF proposed to be due to its inhibition of the Ito current and reducing endo-epicardial electrical gradient as antiarrhythmic mechanism (Haïssaguerre *et al.*, 2009), would be needed to direct specific AAD development and therapy in these conditions.

4.2.3.4. Lessons from previous trials

The sobering tales of CAST and SWORD trials where AADs with known antiarrhythmic mechanisms and proven efficacy when applied to the wrong patients showed that it could bring disastrous outcomes. These studies have been invaluable in educating the arrhythmia community and have been the harness which has both been guiding and slowing the development of new AADs. Dronedarone was a recent new AAD developed with the backbone of the most potent AAD, amiodarone with the intention to retain its antiarrhythmic properties but to avoid the side effects by eliminating the iodine moieties that cause thyroid dysfunction. It was found, pharmacodynamically, to be a multichannel blocker with antiadrenergic properties and it prolongs APD and reduces heart rate, with low risk of torsade de pointes (Dobrev & Nattel, 2010). It was put through its paces in a number of clinical studies before coming to the ATHENA trial (Hohnloser *et al.*, 2009) which showed that the primary outcome of first admission for cardiovascular events or death from any cause was significantly reduced (by 24% compared to placebo) in patients with paroxysmal or persistent AF with additional risk factors. This is despite the fact that Dronedarone was much less efficacious an AAD than amiodarone but yet subgroup analysis identified a

significant reduction in stroke (by 34%) with dronedarone, an effect which was independent of concomitant anticoagulant or antiplatelet agents. This led to the PALLAS trial aimed at investigating the use of dronedarone in high risk permanent AF patients but the study was stopped for safety reasons, with dronedarone causing significant increases in the risk of cardiovascular deaths (by 111%), arrhythmic deaths (by 226%), stroke (by 132%) and hospitalisation for heart failure (by 91%) (Connolly *et al.*, 2011). The positive perceptions from the earlier benefits seen in non-permanent AF patients in ATHENA were wiped out by the depressing results in high risk permanent AF patients in PALLAS and the clinical enthusiasm of this first AAD for 25 years (since CAST) took a significant downturn with very restricted recommendation for clinical application (Camm *et al.*, 2012).

These lessons from clinical trials highlight the complexities involved and the challenges faced in the attempt to tamper with nature's cardiac electrical machinery using AAD to target arrhythmogenic mechanisms. Even drugs that are developed and purported to have specific actions on a single ion channel can have significant effects on others. We have recently shown that the drug ivabradine, which is regarded as a pure I_f channel blocker, can also block hERG K^+ channels and caused APD prolongation and steepening of APDR slope in isolated hearts (Melgari *et al.*, 2015). Much work still needs to be done in understanding the precise mechanisms of specific arrhythmias in the context of disease states with insight from simulation studies and relevant biological models and preparations before the cautious execution in well-planned clinical trials.

5. Conclusions

Selection of AAD in the prevention and treatment of arrhythmias continue to pose challenge. Many AADs have actions on different myocardial ion channels and the presence

of remodelling changes in disease states make it important that specific drug actions are understood and unwanted adverse interactions avoided. Mechanisms underlying atrial and ventricular fibrillation are complex but the improved understanding in the important electrophysiological dynamics of electrical restitution, wavebreak and rotors provide valuable avenues to explore actions of drugs currently available and for future drug development.

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Table 1. Vaughan Williams and Singh classification of AADs and their main electrophysiological actions

Class I: Fast sodium (Na^+) channel blockers

- Ia -Quinidine, procainamide, disopyramide
(depress phase 0, prolonging repolarization, intermediate unbinding kinetics)
- Ib -[Lidocaine](#), [phenytoin](#), [mexiletine](#)
(depress phase 0 selectively in abnormal/ischemic tissue, shorten repolarization, rapid unbinding)
- Ic -[Flecainide](#), [propafenone](#), moricizine
(markedly depress phase 0, minimal effect on repolarization, slow and incomplete unbinding)

Class II: Beta-blockers

- Propranolol
 - Esmolol
 - Timolol
 - Metoprolol
 - Atenolol
- (all decrease slope of phase 4)

Class III: Potassium (K) channel blockers

- Amiodarone (prolongs phase 3; also acts on phases 1, 2, and 4)
- Sotalol (prolongs phase 3, decreases slope of phase 4)
- Ibutilide (prolongs phase 3)
- Dofetilide (prolongs phase 3)

Class IV: Slow calcium (Ca) channel blockers

- Verapamil (prolongs phase 2)
- Diltiazem (prolongs phase 2)

Class V: Variable mechanism

- Adenosine
- Digoxin
- Magnesium sulphate

Table 2. Studies on the effects of drugs and pharmacological agents on cardiac fibrillation dynamics with A. predominant effects on APDR, B. predominant effects on rotor dynamics and C. combined APDR and rotor dynamic effects.

Drug	Reference	Preparation	APD	APDR	CV	Other EP mechanism	Fib→stable	Fibrillation susceptibility	VF / Rotor Frequency	PS density	Core area		
A. APDR predominant effects													
Verapamil	(Riccio, Koiler, & Gilmour, 1999)	2D ventricular endocardial canine prep	↔	↓		↓alternans	yes	↓ Freq variance	↔				
DAM			↓	↓		↓alternans	yes	↓ Freq variance	↔				
Procainamide			↔	↔		↔↔alternans	No	↔↔Freq variance	↓				
Bretylium	(Garfinkel et al., 2000)	Perfuse swine RV prep	↑	↓			yes	↓ initiation					
Amiodarone	(Omichi et al., 2002)	Swine RV	↑	↓			yes	termination	↓		↑		
Propranolol	(Pak et al., 2003)	Rabbit hearts		↓	↓	↓APDRdisp	yes		↓				
Sotalol + Procainamide	(Jin, Chen, Smith, Ideker, & Huang, 2008)	Open-chest swine hearts		↓	↓				↓				
Amiodarone	(Osaka, Yokoyama, Hasebe, & Kodama, 2011)	Human patients	↑	↓	↓CVrest			↓ initiation					
Quinidine	(Ashino et al., 2011)	Brugada patients	↑	↓				↓ initiation					
Ibutilide			↑	↔									
Ranolazine	(Morita et al., 2011)	Isolated Rat hearts		↓		↓EAD	yes	termination					
GS967	(Pezhounman et al., 2014)	Isolated Rat hearts	↓	↓		↓EAD / ↓DAD ↓APDdisp		↓ initiation					
Procainamide	(Osadchi, 2014)	Guinea-pig hearts	↑	↑				Spontaneous VT					
Lidocaine				↔				No VT					

Drug	Reference	Preparation	APD	APDR	CV	Ionic / EP mechanism	Fib→stable	Fibrillation susceptibility	VF / Rotor Frequency	PS density	Core area	
<i>B. Rotor predominant effects</i>												
Tetrodotoxin	(Mandapati et al., 1998)	Rabbit heart							↓	↓	↑	
Verapamil	(Samie et al., 2000)	Rabbit heart							↓	↓	↑	
Quinidine	(Noujaim et al., 2011)	HEK cells / mouse hearts				Partial IK1block		No termination	↓			
Chloroquine						IK1 block		Termination	↓			
<i>C. APDR and Rotor effects</i>												
Ibutilide	(JIN et al., 2012)	Open chest canine hearts	↑	↓		↓APDRdisp		↓DFT	↓			
Tertiapin	(Bingen et al., 2013)	Neonatal rat and intact atria	↑	↓	↓ CVrest	IKAch block		↓ initiation	↓	↓		
Apamin	(Hsieh et al., 2013)	Normal rabbit Failing rabbit	↔ ↑	↔ ↓					↓	↓		

Figure Legends

Figure 1. A. Diagrammatic representation of the myocardial action potential and the ionic currents at work. The cell membrane is negatively charged during the resting Phase 4. Stimulation of the cell from the incoming electrical impulse opens fast Na^+ channels to allow rapid influx of Na^+ into the cell during Phase 0 with depolarisation (I_{Na}). Phase 1 sees the inactivation of Na^+ channels with early repolarisation from transport of K^+ out of the cell via the transient out current (I_{to}). Phase 2 describes a plateau period where Ca^{2+} transport into the cell (I_{Ca}) is balanced by the continued exit of K^+ out of the cell. During rapid repolarisation in Phase 3, K^+ continue to exit cell [via the rapid (I_{Kr}) and slow (I_{Ks}) component of the delayed rectifier K^+ current] to restore the negative membrane potential and return to the resting Phase 4 (where there is a background inward rectifier K^+ current I_{K1}). B. Diagrammatic representation of the action potential of a pacemaker myocardial cell and the ionic currents at work. During Phase 4, there are a number of currents at work including the hyperpolarisation-activated 'funny' (I_{f}) current, acetylcholine-sensitive K^+ (I_{KACh}) current, the L- and T- type Ca^{2+} currents and the $\text{Na}^+-\text{Ca}^{2+}$ exchange current (I_{NCX}) driven by local Ca^{2+} release, which causes diastolic depolarisation until a threshold is reached with Phase 0 which sees depolarisation driven by entry of Ca^{2+} into the cell via I_{CaL} . Repolarisation is modulated by the delayed rectifier K^+ currents (I_{Kr} and I_{Ks}) and I_{KACh} .

Figure 2. Diagrammatic representation of APD restitution with A. action potential illustrating the timings of diastolic interval (DI) and APD at slow heart rate (long DI). B. With a faster heart rate with shorter DI, APD shortens and during restitution a small change in DI will lead to bigger changes in APD. A slowing of heart rate with the last DI being longer precedes a longer APD at the last beat. C. The relationship between APD and DI can be plotted which usually assumes a mono-exponential curve. The slope during APD restitution can be

measured at the tangent or 1st derivative of the curve. The points corresponding to the situations in A. and B. are marked with the purple and blue symbols respectively.

Figure 3. A. Illustration of APD / DI relationship in the situation where the APD restitution slope is less than 1. The top trace starts with 2 steady state beats, followed by a premature beat (with shorter DI) and subsequent rhythm at the same heart rate which means the sum of APD and DI is constant and follows the straight line described by the equation $CL = APD + DI$. The premature beat with shorter DI gives rise to a shorter APD followed by a longer DI, as the APDR slope is shallow and less than 1, the ensuing APD will be prolonged but to a limited extent, followed by a less shortened DI (compared to the previous beat) and so on where a steady state of stable APD and DI will be arrived. A. Illustration of APD / DI relationship in the situation where the APD restitution slope is greater than 1. As opposed to A, the premature beat gives rise to a short DI and short APD, which following a same heart rate will give rise to a longer DI, longer APD and then a much shorter DI (compared to the previous beat). A situation of alternating long and short APD will arise and the last stimulus lands on a long APD which blocked activation and can set of re-entry or wavebreak.

Figure 4. Diagrammatic representation of electrophysiological properties of Class I AADs. Compared to the baseline APD (black line), Class Ia drug slows the phase 0 AP upstroke and prolongs APD (red), Class Ib drug causes mild slowing of phase 0 AP upstroke and shortens APD, whereas Class Ic drug significantly slows phase 0 AP upstroke but has little effects on APD.

Figure 1.

A

B

Figure 2.

Figure 3.

A

B

Figure 4

7. Conflict of Interest statement

The author declares that there are no conflicts of interest.

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