REVIEW

Antiarrhythmics—from cell to clinic: past, present, and future

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The past two decades have witnessed a rapid growth in understanding of the cellular and molecular basis of both normal and pathological electrophysiology. Elucidation of cardiac ion channel structure and function has contributed to many of these advances. As a result, we may be on the verge of an era where arrhythmia management will no longer be dominated by trial and error based observational treatment. Our aim in this article is to provide an overview of antiarrhythmic drug action, linking known actions at the level of cellular electrophysiology to clinical use. Taking particular examples, we shall also illustrate how molecular genetic advances have shown that some rhythm disturbances can result from specific defects in genes encoding cardiac ion channels. Making reference to investigational drugs under study, we will also consider the issue of whether advances in the understanding of cardiac cellular electrophysiology may improve rational approaches to antiarrhythmic drug design and treatment.

The mechanism of drug action is central to the process of choosing a drug to treat any particular arrhythmia. Thus it is useful to consider first impulse generation at the cellular level. This in turn demands consideration of the ion channels underpinning impulse generation in different cardiac muscle cell types. It is the opening and closing of a range of different ion channels that leads to the distinct profiles of membrane potential which comprise cardiac *action potentials*. Therefore, we shall initially consider the electrophysiological characteristics of cardiac action potentials, aspects of ion channel function, and ion channels as sites of antiarrhythmic drug action.

Membrane and action potentials: conventions

Figure 1 shows schematic representations of action potentials from pacemaker, ventricular, and atrial tissues. Whereas the membrane potential in pacemaker cells (typically from the sinus node, as this is usually the dominant pacemaker) constantly cycles (fig 1A), cells (myocytes) from ventricular (fig 1B) and atrial tissue (fig 1C) possess true *resting potentials*, which usually lie between -70 and -80 mV. The negative value of the resting potential reflects the dominant effect of a steady net efflux of positively charged K^+ ions in these cell types by way of an ionic current (I_{K1}), through a channel type called the inward rectifier.¹ Pacemaker cells from sinoatrial² and atrioventricular nodes³ appear to lack a significant I_{K1} , and as a result—along with other ionic currents—they do not show a true resting membrane potential; rather, a *pacemaker potential* precedes each action potential. Action potentials in all cell types result from positive shifts in membrane potential (*depolarisation*), caused by opening of ion channels, allowing positively charged sodium and calcium ions to enter the cell through channels selective for each ionic type. The rate of depolarisation during the action potential upstroke in atrial and ventricular cells is faster than in pacemaker cells, owing to the fact that a large and fast sodium current underlies the upstroke in these cell types, while the upstroke in pacemaker cells is predominantly carried by a calcium current. After the peak of the action potential, the membrane potential is restored to its original value during the *repolarisation* phase, as channels passing depolarising current close and repolarising channels (largely a range of potassium channels) open. Ventricular cells in particular also possess a distinct *plateau* phase, and the relatively long duration of the ventricular action potential helps make the ventricular tissue refractory to overexcitation which might otherwise tetanise the ventricular myocardium. The distinct action potential phases discussed above are sometimes referred to as phases 0 to 4: phase 0 is the action potential upstroke, phase 1 is the early repolarisation “notch” (evident immediately after the ventricular action potential peak in fig 1B), phases 2 and 3 describe plateau and late repolarisation (pacemaker cell action potentials without a distinct

Figure 1 Schematic illustration of representative action potentials from (A) cardiac pacemaker cell, (B) ventricular cell, and (C) atrial cell.

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Figure 2 Ionic and membrane potential gradients determine the direction of ion flow across the cell membrane. (A) Direction of sodium movement (shown by arrow) with normal transmembrane Na gradient. Reversal/equilibrium potential (E_{Na}) is calculated using the Nernst equation (left panel inset shows this for Na at physiological temperature). When transmembrane potential (V_M) is less positive than E_{Na} the electrochemical gradient favours Na entry (left panel). Right panel: If V_M exceeds E_{Na} (for example, by depolarising the cell beyond E_{Na} —illustrated by +++), the electrochemical gradient favours sodium exit. (B) Direction of potassium movement (shown by arrow) with normal transmembrane K gradient when V_M is more positive than E_K (left panel) and more negative than E_K (right panel; -- represents applied hyperpolarisation).

notch or plateau may lack distinct phases 1 and 2), while phase 4 is the period after repolarisation is complete (the resting level in non-pacemaker cells, and the pacemaker depolarisation in pacemaker cells).

Ion channels: the basics

Critical to action potential generation is the combined function of different membrane bound ion channels, together with ion exchange proteins and ATP driven pumps. ATPases for Na/K^+ and Ca^{2+} help sustain the normal transmembrane gradients for these ions, and a sodium–calcium exchange protein contributes to calcium and sodium homeostasis and membrane potential generation (for example, Allen and colleagues,⁶ Janvier and Boyett⁷). To understand modifications of ionic currents by antiarrhythmic drugs, some basic properties of ion channel function need to be examined. In simple terms, transmembrane ion channels activated by membrane potential changes can be viewed as proteins comprising a voltage sensor coupled to a pore through which ions flow; the pore incorporates a “selectivity filter” which determines which types of ions will pass through the open pore.

FLOW OF IONIC CURRENT IN RELATION TO “EQUILIBRIUM POTENTIAL”

The direction of ion flow (and therefore of electrical current generation) is determined by the transmembrane concentration gradient

established by the concentrations C_o outside and C_i inside the cell of the permeant ion, together with the electrical gradient resulting from the membrane potential.

For a particular ionic species and given values of C_o and C_i , there will be one membrane potential value (termed the “equilibrium potential” E_{ion} , and calculable using the Nernst equation—see inset fig 2A, left panel), at which there is no net driving force for ions to flow across the membrane. For example, for sodium ions E_{Na} lies near +70 mV; at potentials negative to this, sodium ions will flow down their concentration gradient (from outside to inside the cell) and generate a *depolarising* or inward current (fig 2A, left panel). Beyond E_{Na} (a situation encountered experimentally, but not physiologically), sodium ions would flow in the opposite direction (fig 2A, right panel). Conversely, for potassium ions, E_K lies near −90 mV, and at potentials positive to this potassium ions will flow down their concentration gradient (from inside to outside the cell) and generate *repolarising* or outward current (fig 2B, left panel). If the inside of the cell is made more negative than E_K the direction of ion flow will be reversed (fig 2B, right panel). With a knowledge of the normal intracellular and extracellular ion concentrations, it is possible to predict the contributions of sodium, calcium, and potassium channels in generating membrane potential depolarisation or repolarisation.

CHANNEL GATING

One further aspect of ion channel function should be covered before considering the roles played by individual ion channel types—*channel gating*. Voltage operated channels are usually referred to as voltage gated, as biophysical measurements indicate that specific membrane potential regulated processes determine the magnitude and time course of ionic current flow across the range of ion channel types. This can be explained by considering an ion channel that does not pass current until a depolarising stimulus is applied. At rest, the channel is therefore considered to be closed (fig 3A). When a depolarising stimulus is applied, the membrane potential change is detected by the voltage sensor—the channel undergoes a conformational change and opens in order to allow ionic current to flow (fig 3A). The process describing the transition from the closed to open state is termed *activation*. The probability of channels moving to the open state usually depends on the magnitude of the voltage change (activation is therefore “voltage dependent”), and the speed with which channels move from the closed to the open state will determine the rate of activation.

Some voltage dependent channels show only a voltage dependent activation process, but for many a second process also influences ionic current flow. If the depolarising stimulus is maintained, a second conformational change occurs in the ion channel. Part of the ion channel protein moves to occlude the channel pore such that, while the channel may be fully activated, it becomes poorly conducting (fig 3A).

Figure 3 (A) Ion channels undergo changes in protein conformation that determine whether ionic current flows or not. At rest channels are closed (C), but when an appropriate stimulus is applied (a change in membrane potential for voltage operated channels, an appropriate ligand, for example, acetylcholine, for ligand operated channels), the channel conformation changes (during a process called “activation”; C→O) to allow the relevant ion to pass through the channel pore, here shown for ions passing from inside to outside of the cell. Many voltage operated channels undergo a second transition; in the presence of a sustained depolarising stimulus, the channel conformation undergoes a further change to prevent current flow—this process is called inactivation (O→I). Inactivation can occur in two ways; either a blocking particle moves to occlude the internal face of the channel pore (N type inactivation), or a change to the outer portion of the channel pore prevents ion flow (C type inactivation). The net result is that ions can no longer pass through the channel pore. (B) Measurements of ionic current from heart cells are made using voltage or patch clamp methods. These techniques allow detailed study of drug–channel interactions. To introduce ionic current records to the reader unfamiliar with this technique, we present example currents, recorded from an individual ventricular myocyte using whole cell patch clamp. The membrane potential is controlled by the experimenter, allowing measurements of whole cell membrane current to be made in response to applied voltage commands. In this example, the cell membrane potential is held at -80 mV and a double step pulse applied. The first step to -40 mV elicits a large and brief downward current deflection. This represents a large, rapidly activating and inactivating current through Na channels. The second step to $+10$ mV elicits a second downward deflection (of smaller amplitude than I_{Na}), which then gradually returns to baseline during the command step. This represents current flow through L type Ca channels and shows that $I_{Ca,L}$ activates quickly, and then subsequently inactivates (at a slower rate than inactivation of I_{Na}). Both $I_{Ca,L}$ and I_{Na} are inward or depolarising currents. A current deflection in the opposite direction (with an amplitude positive to 0 on the current axis) would represent an outward, or repolarising current.

This process, which, like activation, is voltage and time dependent, is termed *inactivation*. Experimentally, the properties of channel activation, inactivation, voltage sensitivity, and ionic selectivity can be studied using voltage or patch clamp techniques. (An example of ionic current profile measured using these techniques is given in fig 3B.)

The important points here are as follows:

- Distinct ion channel types generate depolarising and repolarising currents during the action potential.
- From the existence of distinct ion channels with distinct roles arises the potential for drug classification and design.
- The fact that ion channels undergo voltage dependent state transitions (fig 3A) means that, theoretically, drugs could bind to resting/closed (C), activated/open (O) or inactivated (I) states.⁸

Drugs which bind preferentially to open or inactivated channel states may exert effects that vary with stimulation frequency (or in vivo, with heart rate) and as such can show *use dependence*. For antiarrhythmic agents, an ideal channel blocking agent would have positive use dependence—showing a greater inhibitory action at faster heart rates. Drugs binding preferentially to closed channels may either exert use independent actions or show “reverse use dependence,” in which the drug dissociates from its binding site during channel activation. With reverse use dependent blockade, faster rates of channel stimulation (or indeed heart rate) encourage greater dissociation than slower rates, resulting in comparatively less channel inhibition at faster than at slower rates.

Ion channels as antiarrhythmic drug targets

CHANNELS INVOLVED IN PACEMAKING

In the sinus node, the T type calcium current ($I_{Ca,T}$) and the hyperpolarisation activated current (I_h) both provide inward, depolarising current during the pacemaker depolarisation² that precedes each action potential upstroke (fig 1A). Agents that reduce these currents should therefore slow the rate of the pacemaker depolarisation and thereby have a negative chronotropic effect. Specific inhibitors of I_h produce rate reduction.^{9–10} Mibefradil is a blocker of $I_{Ca,T}$ which preferentially relaxes coronary vasculature and slows heart rate without reducing contractility,¹¹ making it a potential bradycardic agent. This particular compound was voluntarily withdrawn because it was involved in several clinically relevant drug interactions.¹² In general, the use of selective bradycardic agents is likely to be of limited value except in inappropriate sinus tachycardia.

CHANNELS INVOLVED IN ACTION POTENTIAL DEPOLARISATION

L type calcium and sodium channels are of greater importance as antiarrhythmic targets. $I_{Ca,L}$ appears to be the dominant depolarising current during action potentials from the sinoatrial² and atrioventricular (AV) nodes.^{3–13} The dependence of AV nodal conduction on $I_{Ca,L}$ makes L type channel blockers such as verapamil and diltiazem important in the management of supraventricular tachycardias. In paroxysmal atrioventricular tachycardias, either anterograde or retrograde conduction through the AV node forms part of the circuit maintaining the arrhythmia; thus blockade of $I_{Ca,L}$ can be effective in preventing recurrence of

the arrhythmia.^{14–16} L type channel blockers can also be effective against AV nodal reentrant tachycardias¹⁴ and atrial fibrillation.¹⁷

The importance of I_{Na} in generating the fast upstroke phase of both atrial and ventricular action potentials makes I_{Na} blockers potentially effective against both supraventricular and ventricular arrhythmias. Sodium channel–drug interactions are usefully considered within the “modulated receptor” model, which takes into consideration the channel state to which a drug preferentially binds.^{8, 18} The action potential upstroke rate can become slowed when I_{Na} is reduced and as a result I_{Na} blockers can decrease impulse conduction velocity. In addition, agents that delay the recovery of I_{Na} from channel inactivation have the effect of prolonging tissue refractoriness.

Agents such as quinidine,¹⁹ propafenone,²⁰ and disopyramide²¹ preferentially bind to the open (activated) state of the sodium channel, while others including lignocaine (lidocaine)²² and mexiletine²³ show a preference for the inactivated channel. Open channel blockers are effective in generally reducing electrical excitability and impulse conduction, while inactivated channel blockers may show a blocking effect influenced by differences in atrial and ventricular action potential profile (fig 1). The comparatively longer and more depolarised ventricular action potential plateau results in a more prolonged inactivation of I_{Na} , with an increased level of block. This property may contribute to the selectivity of drugs such as mexiletine against ventricular arrhythmias; it might also be used in combination treatment by combining an inactivated state sodium channel blocker with a drug that delays repolarisation,²⁴ resulting in enhanced sodium channel inhibition and thereby prolonged refractoriness.

The kinetics of recovery from block are also critically important in determining the effects of sodium channel blockers. Agents associated with slow recovery from block (for example, flecainide²⁵) cause a block that accumulates rapidly on repetitive stimulation, and a stable steady state level of block is attained over a wide range of heart rates.²⁶ Agents with relatively fast recovery from block (for example, mexiletine) may show little cumulative block at slow heart rates, as block is relieved between action potentials. At faster rates (tachycardias), block accumulates because there is too little time for unbinding to occur between action potentials. This produces the effect of “positive use dependence,” which is beneficial in that little ECG alteration may be experienced at normal rates, whereas drug effects become important during tachyarrhythmias.

It is important to realise, however, that blocking efficiency and recovery can be affected by various factors. Open channel blockers may be less effective in damaged or ischaemic tissue; this is often depolarised, resulting in the inactivation of a proportion of channels, thereby rendering these unavailable for block. In contrast, inactivated state blockers may be more effective in conditions where tissue

becomes depolarised—experimental evidence suggests that the efficacy of lignocaine and the risk of proarrhythmia are both enhanced in acutely ischaemic myocardium.²⁷ In addition to the effects of membrane potential depolarisation on block, the low pH associated with ischaemia can also slow the time constant of drug dissociation, enhancing the cumulative level of channel block.²⁶

POTASSIUM CHANNELS

Some sodium channel blocking agents, for example disopyramide²⁸ and in particular quinidine,²⁹ are also associated with delayed repolarisation and QT prolongation on the ECG. For both disopyramide³⁰ and quinidine,^{31, 32} this effect results from potassium channel blocking actions of the drug. Excessive action potential and QT prolongation (when the corrected QT interval (QT_c) exceeds ~440²⁹ to 460³³ ms), carries a risk of proarrhythmia. However, potassium channel blockade can also be antiarrhythmic, because moderately delayed action potential repolarisation can enhance the inactivation of depolarising currents (I_{Na} and I_{Ca}), thereby prolonging the period between successive action potentials. This can be effective in disrupting arrhythmias caused by reentrant mechanisms. Different potassium channel types, therefore, offer potential antiarrhythmic drug targets. Major potassium ion channel types involved in action potential repolarisation include the transient outward current, I_{To} , responsible for the action potential notch in ventricular cells and prominent during atrial repolarisation.^{1, 34} The rapid and slow components of delayed rectifier current (I_{Kr} and I_{Ks} , respectively³⁵) are important in plateau repolarisation.^{36, 37} The inward rectifier potassium current is important for the final stage of repolarisation^{37, 38} and for maintaining the cell resting potential. Owing to their roles in plateau repolarisation, I_{Kr} and I_{Ks} are of particular interest as antiarrhythmic targets.

As in the case of sodium channel blocking agents, the desirable potassium channel blocker is one that shows positive use dependence (that is, the drug effects are greatest at faster action potential rates). Unfortunately, many potassium channel blocking drugs appear to be associated with a *reverse* use dependent effect: action potential prolongation is greater at slower rather than at faster rates.³⁹ The problem with this is that action potential prolongation at slow rates can be proarrhythmic through the cellular mechanism of early afterdepolarisations. By a mechanism originally investigated by January and Riddle⁴⁰ and recently reviewed by Makielski and January,⁴¹ sufficiently slowed membrane repolarisation during the action potential facilitates calcium entry through L type calcium channels, which can result in early afterdepolarisations. These in turn could give rise to triggered activity and lead to torsade de pointes. Selective block of I_{Kr} (for example, by the drug E-4031) can be sufficient to induce early afterdepolarisations.⁴² Early afterdepolarisations are relieved at faster rates; therefore I_{Kr} block is most likely to be

proarrhythmic at slow rates. The clinical implications of reverse use dependence and specific I_{Kr} block are exemplified by sotalol which, as the racemic D-L mix, possesses β blocking and I_K blocking actions and is indicated for the treatment of life threatening ventricular tachycardia. Racemic sotalol produces some QT prolongation and is bradycardic.⁴³ D-sotalol lacks the β blocking activity of the racemic mix, but is an I_{Kr} blocker³⁵ and shows reverse use dependent effects on the action potential.⁴⁴ Significantly, D-sotalol is associated with an increased risk of death from presumed arrhythmias.⁴⁵

A simple explanation for reverse use dependent drug effects on action potential prolongation involves drug binding to the resting channel (in the interval between action potentials) and dissociating during membrane depolarisation.⁴⁶ This would produce a greater relief of block at faster rates (at which there would be shorter intervals between action potentials for drug binding to occur). However, subsequent experiments on cloned channels are not consistent with this explanation (for example, Synders and colleagues⁴⁷). Moreover, agents such as almokalant block I_{Kr} in a use dependent fashion,⁴⁸ while producing reverse use dependent action potential prolongation.²⁴ In addition, dofetilide has been reported to produce rate independent effects on I_{Kr} , but reverse rate dependent effects on the action potential.⁴⁹ In the same study,⁴⁹ repetitive stimulation was observed to increase the magnitude of I_{Ks} but not of I_{Kr} . It has been proposed, therefore, that reverse use dependence may result from the interaction between I_{Kr} and I_{Ks} during repolarisation at different heart rates.⁴⁹ At slower rates I_{Kr} may be dominant; at faster heart rates the role of I_{Ks} increases owing to incomplete deactivation (the transition of channels from O→C, fig 3A) of the current between action potentials. Thus specific I_{Kr} inhibition would have a greater effect on repolarisation at slower than at faster rates.

If this mechanism holds, then an agent which blocks I_{Ks} specifically might be better for treating tachycardias than an I_{Kr} blocker; moreover, an agent that blocks both components of I_K might have an improved safety profile over a specific I_{Kr} blocker. There are few experimental data yet available to support the first of these possibilities (selective I_{Ks} blockers are only beginning to appear); the second, however, does seem to hold true. Quinidine and sotalol do not appear to block I_{Ks} .⁵⁰ By contrast amiodarone, which has a much better cardiac safety profile, blocks both I_{Kr} and I_{Ks} .^{50, 51} while also showing a more consistent effect on action potentials at different rates.⁵²

A further potassium channel should be mentioned, as it is likely to mediate the antiarrhythmic actions of adenosine. The extremely short half life of adenosine makes intravenous administration valuable in terminating tachycardias involving the AV node (either AV nodal re-entry or AV re-entry). In bolus form, adenosine has been shown to be highly effective against paroxysmal supraventricular tachycar-

dias that require AV nodal conduction for their maintenance.^{53, 54} The cellular basis for the effect of adenosine appears to resemble that for acetylcholine. Acetylcholine activates a potassium current (I_{KACh}), which is important in mediating parasympathetic effects on the sinoatrial² and AV nodes.⁵⁵ When activated, I_{KACh} produces membrane potential hyperpolarisation; it thereby decreases automaticity and excitability. At the cellular level, adenosine activates a current (I_{KAAdo}) with properties identical to those of I_{KACh} (for example, Belardinelli and colleagues⁵⁶). Cellular studies on rabbit AV node suggest that activation of I_{KAAdo} is likely to be predominantly responsible for the action of adenosine, with possible supplementary effects on L type calcium channels.^{57, 58}

Molecular insights into arrhythmogenesis

Some of the most exciting cardiological developments of the last decade relate to advances in understanding the molecular biology underlying ion channel function, and the finding that defects in individual ion channels can underlie particular arrhythmias. This is no better exemplified than in congenital long QT syndrome. This syndrome illustrates how various different channelopathies can manifest themselves clinically as virtually identical electrocardiographic endpoints. Congenital long QT syndrome is characterised by abnormally prolonged ventricular repolarisation leading to QT_c prolongation (as discussed earlier), with an associated risk of malignant ventricular tachyarrhythmias (torsade de pointes).

Congenital long QT syndrome has been found to arise from a range of different genetic abnormalities^{33, 59-67} (table 1). The two main forms are the autosomal dominant Romano-Ward syndrome (pure cardiac phenotype)⁶⁸ and the autosomal recessive Jervell-Lange-Nielsen syndrome (in which cardiac abnormalities coexist with congenital deafness).⁶⁹ Of the genetic abnormalities identified in the Romano-Ward syndrome, four are associated with identified ion channels (table 1). Most of the mutations causing congenital long QT (LQT) syndrome are missense mutations. However, substantial phenotypic heterogeneity remains, even with identical gene abnormalities. LQT1, 2, and 3 all result in prolongation of the action potential. The extent of prolongation depends not only upon the gene mutated, but also upon the exact location of the mutation.^{33, 70} As discussed earlier, it is the risk of afterdepolarisations associated with QT interval prolongation—rather than slowing of action potential repolarisation on its own—that is arrhythmogenic. The involvement of L type I_{Ca} in the production of early afterdepolarisations and the widely known enhancement of I_{Ca} by β adrenergic stimulation may, at least in part, explain the clinical effectiveness of β blockers in reducing the incidence of syncopal episodes and arrhythmias in the long QT syndrome.^{33, 70}

As shown in table 1, alterations in the genes underlying I_{Kr} and I_{Ks} are associated with LQT-2 and LQT-1. The channels for both I_{Kr} and I_{Ks} are multimeric,³⁶ and alleles from both

Table 1 Congenital long QT syndrome

Locus of genetic defect	Molecular defect	Functional manifestation of defect	Possible treatment
LQT-1: chromosome 11	KvLQT1 mutation reduces I_{Ks}	Increased APD; EAD triggers activity	<ul style="list-style-type: none"> ● Increase I_{Ks} ● β Blockers ● Increase outward or decrease inward currents
LQT-2: chromosome 7	HERG mutation reduces I_{Kr}	Increased APD; EAD triggers activity	<ul style="list-style-type: none"> ● Increase I_{Kr} ● β Blockers ● Increase outward or decrease inward currents
LQT-3: chromosome 3	SCN5A mutation increases I_{Na}	Increased APD; EAD triggers activity	<ul style="list-style-type: none"> ● Block late opening Na channels with mexiletine or lignocaine ● β Blockers ● Increase outward currents ● As yet unknown
LQT-5: chromosome 21	KCNE1 protein (min K) mutation (ancillary subunit for I_{Ks} channel complex)	Increased APD; EAD triggers activity	—
Chromosome 4	As yet unknown	—	—

APD, action potential duration; EAD, early after depolarisation; I_{Ks} , slowly activating outward K current; I_{Kr} , rapidly activating delayed rectifier current; LQT, long QT; SCN5A, gene for the cardiac Na channel.

parents contribute to the channel complexes. Mutant channels expressed in oocytes or cell lines show loss of function.⁶¹ Channel kinetics, as well as reduced overall current, contribute to the loss of function (that is, a reduction in repolarising outward current). In contrast, mutations of sodium (SCN5A) channels cause a gain of function,^{71–72} in which a late persistent (depolarising) sodium current is produced because of defective inactivation of I_{Na} . Owing to the heterogeneous basis for congenital long QT syndrome, identification of the underlying cause is pivotal in deciding upon appropriate treatment. Provocation may distinguish between the different congenital LQT syndromes. While the QT interval shortens only minimally with exercise in LQT1 and LQT2, in patients with LQT3 it shortens significantly.^{70–73} Furthermore, torsade de pointes is precipitated by adrenergic stimulation (for example, during exercise) in LQT1, possibly because I_{Ks} normally predominates at high rates, and therefore reduced I_{Ks} would lead to inadequate shortening of the action potential.⁷⁰ In contrast, most patients with LQT 3 experience more events at rest than on exertion.^{70–73}

Another interesting group of patients providing a clear link between cellular abnormalities and clinical treatment are those with the Brugada syndrome.^{74–75} These patients have structurally normal hearts and right precordial ST segment elevation or right bundle branch block.⁷⁶ The ECG abnormalities probably reflect exaggerated transmural differences in action potential configuration, especially within the right ventricular outflow tract. The end result is an increased risk of ventricular fibrillation within these families. One variant of the Brugada syndrome arises from a mutation of the SCN5A gene (the same gene that is implicated in LQT3),⁷⁷ leading to a gain of function; hence drugs targeting the sodium channel may be clinically effective.

IMPLICATIONS OF GENETIC INSIGHTS?

In addition to the syndromes described above, our understanding of the role of genes in other conditions has also increased. The reader is referred to a recent and comprehensive review by Priori and colleagues.⁷⁰ A clear result of the

arrival of molecular biology in the clinical arena is that genetic testing may be available not only for diagnostic purposes in patients presenting with arrhythmias but also possibly for individuals who could benefit from prophylactic treatment to avoid sudden death. Increased genetic knowledge may also influence treatment strategy. For example, sodium channel blockers such as lignocaine and mexiletine may be effective in LQT-3,^{71–72} while LQT-2 would be expected to respond to a different approach. Cloned channels encoded by HERG (the gene underlying channels for I_{Kr}) show currents that increase in size as external potassium concentration ($[K]_o$) is raised and decrease as $[K]_o$ is lowered.⁶⁰ Consistent with this experimental observation, Compton and colleagues⁷⁸ have shown that abnormal repolarisation in patients with LQT-2 can be corrected by raising serum potassium.⁷⁸

However, while long QT syndrome and the Brugada syndrome may provide a clear route from cell to clinic, some common arrhythmias are not yet so accommodating. Refractory arrhythmias, for example, may be refractory because of the complex processes involved in their pathogenesis. These may include both electrical and structural remodelling. Electrical remodelling may be physiological and unrelated to cardiac disease (for example, atrial fibrillation may become self sustaining⁷⁹), or pathological in origin (alteration in the distribution of gap junctions between cells in diseased tissue⁸⁰). Structural remodelling may also be either physiological (for example, initial ventricular hypertrophy in response to hypertension) or pathological (cell hypertrophy in peri-infarct zones and cell loss with replacement fibrosis within infarcted regions⁸¹). Therefore complex arrhythmias with a multifactorial aetiology may benefit from primary prevention targeted towards alleviation of diseases such as coronary occlusion or ventricular hypertrophy. A second line of attack may then be directed towards the electrophysiological sequelae of upstream events. Treatment must be tailored towards the aetiology of the arrhythmia, as drug treatment for ventricular tachycardia in one patient may be detrimental in another. Indeed, in the structurally abnormal heart—for example, after

myocardial infarction or during congestive cardiac failure—drug efficacy has been limited and in these conditions antiarrhythmic drugs can have a significant proarrhythmic potential.^{82–84}

Re-evaluation of antiarrhythmic drug classification

Another area that has experienced change owing to the increased information available from cellular cardiology is that of drug classification. Early approaches to antiarrhythmic drug development involved the identification of natural compounds with antiarrhythmic activity such as cinchona,⁸⁵ or identification of antiarrhythmic effects of drugs licensed for other uses, primarily local anaesthetics, including lignocaine and its derivatives. Clinical studies verified the acceptability as antiarrhythmic agents of synthetic molecules such as procainamide.⁸⁶ Further attempts were then made to produce related compounds with increased potency and reduced toxicity (for example, flecainide, lorcinide, and encainide^{82–87}). While this approach has provided many useful drugs for therapeutic use, the derived compounds have to varying degrees retained the adverse effect profiles of parent drugs. Progress in the development of newer antiarrhythmic drugs has not been as great as once anticipated, and the chance discovery of antiarrhythmic properties of drugs developed for other conditions—for example, amiodarone (initially developed as an antianginal drug)—has contributed significantly to the armoury available to the clinician.

In 1970, Vaughan Williams proposed a classification based on possible ways in which abnormal cardiac rhythms could be corrected or prevented.^{88–89} In this early classification, class I drugs act by reducing inward sodium current at concentrations not affecting the resting membrane potential. Class II drugs act by blocking sympathetic activity of the heart. Although not thought to affect the action potential of most

myocardial cells, these drugs reduce the spontaneous rate of depolarisation of pacemaker cells under adrenergic stimulation and are therefore negatively chronotropic. They are also negatively dromotropic, as the AV node tends to be under greater sympathetic drive than the sinoatrial node for which vagal tone normally predominates. Class III drugs prolong action potential duration. They do not specifically affect any single factor involved in repolarisation (although in reality most class III drugs exert potassium channel blocking actions). They are able to alter the activity of several different ion channel conductances at a cellular level, making their impact upon the action potential quite complex. In general, they prolong action potential duration and hence prolong the length of the refractory period. In a separate class was placed diphenylhydantoin, a centrally acting drug.

In 1974, Singh and Hauswirth modified the classification, with two major changes.⁹⁰ First, lignocaine and diphenylhydantoin were placed in a separate class, because at low concentrations and at low external potassium concentrations, they had little effect upon the action potential or cardiac conduction. Secondly, a separate class (now denoted class IV) was introduced to accommodate calcium channel blockers, which (as described earlier) predominantly affect regions in which action potential depolarisation depends on $I_{Ca,L}$. In a further development, class I drugs were subclassified by Harrison⁹¹ according to their effect upon action potential upstroke and duration. Additional studies^{87–92–93} showed that the subclassification separated class I drugs according to the rate of recovery of I_{Na} channels from blockade. Class 1a drugs were intermediate between class 1b drugs, with fast recovery time constants less than one second, and class 1c drugs, with relatively slower recovery time constants of more than 15 seconds.

The “Singh-Hauswirth-Harrison-Vaughan Williams” (S-H-H-VW) classification is summarised in table 2. Many antiarrhythmic drugs have more than one class of action (for

Table 2 Singh-Hauswirth-Harrison-Vaughan Williams (S-H-H-VW) classification system for antiarrhythmic agents

Class of drug	Examples	Primary sites of action	Mechanism(s)	Uses
1a	Quinidine, procainamide, disopyramide	HP, A, V	Slow dV/dt of phase 0; moderate prolongation of repolarisation and PR and QRS duration	SVT and VT
1b	Lignocaine, mexilitine, phenytoin	V	Limited effect on dV/dt. Shortens repolarisation and hence QT interval	VT, VF
1c	Flecainide, encainide, propafenone	HP, V	Slows dV/dt. Little effect on repolarisation. Marked prolongation of PR and QRS intervals	SVT and VT
2	β Blockers, eg propranolol, esmolol	SAN, AVN	Slow rate of rise of phase 4 of the action potential and thus slow discharge of the SAN and AVN. Also suppresses catecholamine induced increase in pacemaker current, delayed rectifier (I_{Kr}), Ca current, and Na current	Tachyarrhythmias
3	Amiodarone, sotalol	A, V, AVN, SAN, HP, AccP	Increase APD by blocking the delayed rectifier current and generally reduce automaticity. SAN and AVN rates are slightly suppressed.	AF, A flutter, SVT, nodal tachycardias, VT, VF prophylaxis
4	Calcium channel blockers, eg verapamil	AVN	Depress phase 2 and 3 of the action potential by blocking the slow Ca current. Note risks from negative inotropism	Atrial tachyarrhythmias

A, atrium; AccP, accessory pathways; APD, action potential duration; AVN, atrioventricular node; HP, His-Purkinje system; SAN, sino-atrial node; V, ventricle.

Table 3 Sicilian Gambit classification of arrhythmogenic mechanisms

Automaticity	Enhanced normal Abnormal
Triggering	Early after depolarisation (depolarisation during the plateau phase) Delayed after depolarisation
Sodium dependent re-entry	Primary impaired conduction (long excitable period) Conduction impaired by refractory period (short excitable period)
Calcium dependent re-entry	
Reflection	
Parasystole	

example, racemic sotalol has class II and class III activity and amiodarone has class I–IV actions). Moreover, some drugs within a particular class may differ in their clinical effects owing to subtle (but significant) differences in their mechanism of action at the ion channel level. In addition, there are some antiarrhythmic drugs (for example, digoxin and adenosine) which cannot be fitted into the S-H-H-VW I–IV classification.

While the S-H-H-VW classification has been valuable, the limitations of inadequate correlations between drug mechanism, arrhythmia mechanism, and therapeutic efficacy gave rise to the “Sicilian Gambit” approach to antiarrhythmic treatment. This approach to arrhythmia management, formulated by the European Society of Cardiology working group,⁹⁴ seeks the critical mechanisms responsible for arrhythmogenesis (table 3) to identify a “vulnerable parameter” or “Achilles heel” of the arrhythmia concerned. This would enable the clinician to select a drug on the basis of its mechanism of action and not empirically. This approach complements well those recent advances in our understanding of molecular biology (for example, cloning and sequencing of ion channels and receptors) that have raised hopes for a “target oriented” approach to antiarrhythmic treatment. There are, however, two fundamental issues that might hinder this approach to drug selection. First, an Achilles heel is not always (yet) identifiable for many arrhythmias, and in some cases there may be more than one Achilles heel, some of which are not involved in arrhythmogenesis. In addition, there are drugs classified within the S-H-H-VW classification that have multiple electrophysiological targets; this may preclude them from being selective for any one particular Achilles heel. Second, consideration of drug action based on multiple targets (ion channels, receptors, and second messenger systems) and the “spread sheet” approach advanced in the Sicilian Gambit⁹⁴ generates a degree of complexity absent from the S-H-H-VW classification, and which may hinder acceptance of this approach.⁹⁵ Against this, however, a major advantage of the Sicilian Gambit approach is that it provides a framework within which the ever increasing information on arrhythmogenesis and drug action can be readily accommodated and considered. (for example, Members of the Sicilian Gambit⁹⁶)

A rational future?

Our increasing knowledge of the basic electrophysiological and genetic characteristics of ion channels, the cellular actions of antiarrhythmic agents, their effects on animal models, and the results of clinical trials should help guide future rational drug development and classification. In a recent article,⁹⁷ Camm and Yap summarise attributes for future antiarrhythmic agents, including: appropriate modification of the arrhythmia substrate, suppression of arrhythmia triggers, efficacy in pathologic tissues and states, positive rate/use dependent effects, similar efficacy in oral and parenteral formulations, similar efficacy in arrhythmias and their surrogates, few side effects, and cardiac selective ion channel blockade.

One of the central issues will be whether approaches which focus on a single ion channel target offer more promise than approaches based on compounds with “polypharmacological” (multiple ion channel) effects. Recently discovered ion channels—such as the ultrarapid delayed rectifier (I_{Kur}) in atrial tissue⁹⁸—may offer new, alternative drug targets. Importantly, the reverse use dependence associated with some drugs with class III (predominantly I_{Kr}) blocking actions might be taken as suggesting that either drugs against alternative targets to I_{Kr} or drugs with multiple effects may be superior to selective I_{Kr} blockers alone.

Unfortunately, the emerging picture is not as clear as this. While the results of the SWORD (survival with oral d-sotalol) trial indicate that d-sotalol increases mortality and is therefore unsuitable for use,⁴⁵ the same does not appear to be true for dofetilide. Dofetilide is a potent and selective blocker of I_{Kr} , which, although associated with reverse use dependent effects on the action potential at the cellular level,⁴⁹ has a profile that is not clearly reverse use dependent in humans (for example, Bashir and colleagues⁹⁹). The drug appears to be reasonably well tolerated and at some concentrations is effective at suppressing ventricular tachycardia.⁹⁹ Moreover, its use does not seem to be associated with significantly increased mortality, and with only a low incidence of torsade de pointes.¹⁰⁰ Quite why dofetilide appears to be safer than d-sotalol is not entirely clear, though there is some experimental evidence that the class III effects of d-sotalol are much more sensitive to extracellular potassium levels than those of dofetilide.⁴⁴ At this stage, it would appear premature to rule out selective I_{Kr} blockade as a viable antiarrhythmic strategy.

I_{Ks} blockade may, in principle, offer an attractive alternative or supplementary approach to I_{Kr} inhibition. Azimilide is a relatively new agent effective at inhibiting both I_{Kr} and I_{Ks} .¹⁰¹ Data from experiments in which I_{Ks} blocking effects of the drug on the action potential have been estimated suggested that the I_{Ks} block alone was associated with rate independent action potential prolongation.¹⁰² The overall drug effect on the action potential (involving combined I_{Kr} and I_{Ks} actions) shows some variations between experimental studies, with reports of either some reverse use

dependence^{102–103} or a rate independent action on effective refractory period.¹⁰⁴ Azimilide may be effective against both atrial and ventricular arrhythmias^{101–104} and, while it is too early to comment with certainty on its efficacy and safety in humans, initial signs appear promising.¹⁰¹ Several clinical trials including the ALIVE (azimilide post-infarct survival evaluation) study¹⁰⁵ were ongoing at the time of writing.

Other investigative agents with polypharmacological effects include ibutilide and tedisamil. Ibutilide has an interesting pharmacological profile in that in addition to affecting I_{Kr} it also appears to induce a sustained sodium current, an effect that would be synergistic in prolonging the action potential.¹⁰⁶ Tedisamil blocks I_{Kr} and the transient outward potassium current (I_{To}).¹⁰⁷ It has been shown to be effective against ventricular fibrillation in a rabbit model¹⁰⁸ and it prolongs the monophasic action potential in humans.¹⁰⁹ Dronedarone, an investigational drug related to amiodarone, may be an agent of particular interest.⁹⁷ Like its parent compound, dronedarone may be expected to exert multiple S-H-H-VW effects and thereby have wide ranging efficacy. The results of trials of this and other agents with polypharmacological effects will be important in the debate about whether the future development of antiarrhythmic agents lies in single or multiple ion channel targets. As the underlying basis for the generation and maintenance of particular arrhythmias becomes increasingly understood, so will our understanding of the nature of any associated Achilles heel or vulnerable parameter. This knowledge, together with ongoing revision of drug classification according to target/action, is likely to refine pharmacotherapeutic approaches to clinical arrhythmia management.

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IMAGES IN CARDIOLOGY

Echohistological correlation in *Candida albicans* endocarditis

A 28 year old man with a history of intravenous drug addiction was admitted to hospital with fever of 15 days duration and sudden pain in both legs. Physical examination showed a regular pulse of 130 beats/min and a diastolic murmur compatible with aortic regurgitation. Peripheral pulses were absent in both legs, which were cold and pale. Abdominal echography and computed tomography (CT) showed a mass obstructing the distal abdominal

aorta as well as numerous splenic infarcts. The mass was extracted and cultured. Two days later the patient suddenly developed left sided weakness, and brain CT detected right parietal ischaemic infarction. Blood cultures were positive for *Candida albicans*.

Transoesophageal echocardiography showed a large vegetation (2.5 × 1 cm) attached to the aortic non-coronary cusp, and severe aortic regurgitation (AO aorta; LA, left atrium; LV, left ventricle; RV right ventricle). The vegetation was very mobile as demonstrated by comparing systole (left) and diastole (right). After a third embolism to the left leg the patient underwent surgery to excise the vegetation, and a bioprosthesis was implanted. On histological examination with periodic acid Schiff stain, typical yeast cells and pseudohyphae of *Candida* species were seen (below left). Methenamine silver stain clearly shows yeast and pseudohyphae elements of *Candida* species (below right). Amphotericin B (0.6 mg/kg/day) was given intravenously for four weeks. Cultures then became persistently negative. There were no other complications and the patient was discharged.

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