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Review Series

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Genetics of acquired long QT syndrome

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The QT interval is the electrocardiographic manifestation of ventricular repolarization, is variable under physiologic conditions, and is measurably prolonged by many drugs. Rarely, however, individuals with normal baseline intervals may display exaggerated QT interval prolongation, and the potentially fatal polymorphic ventricular tachycardia torsade de pointes, with drugs or other environmental stressors such as heart block or heart failure. This review summarizes the molecular and cellular mechanisms underlying this acquired or drug-induced form of long QT syndrome, describes approaches to the analysis of a role for DNA variants in the mediation of individual susceptibility, and proposes that these concepts may be generalizable to common acquired arrhythmias.

Introduction

The QT interval on the surface ECG is a representation of repolarization time in the ventricle. QT intervals in humans vary as a function of age, sex, heart rate, heart disease, and drugs and are generally less than 480 ms. "Acquired long QT syndrome" describes not one end of a physiologic spectrum, but rather pathologic QT interval prolongation, generally to greater than 550–600 ms, upon exposure to an environmental stressor and reversion back to normal following withdrawal of the stressor. When QT intervals are markedly prolonged in this fashion, the polymorphic ventricular tachycardia torsade de pointes becomes a real risk; torsade de pointes can be self-limited or can degenerate to fatal arrhythmias such as ventricular fibrillation. It is the potential for torsade de pointes and sudden death that has generated such attention to acquired long QT syndrome (1, 2). As discussed below, the principles elucidated in studies of drug-induced long QT syndrome likely apply broadly to more common arrhythmia phenotypes.

This review focuses on drug therapy, the most common cause of acquired long QT syndrome. Acquired QT interval prolongation and torsade de pointes can occur in other settings, such as heart block (3) and, rarely, acute myocardial infarction (4) (Table 1 and Figure 1). In addition, even minor degrees of QT interval prolongation have been associated with increased mortality in many settings, notably convalescence from acute myocardial infarction (5), advancing age (6), and heart failure (7–9). The extent to which the mechanisms described below apply to these settings is uncertain, although overlap seems likely.

Most recognized cases of drug-induced long QT syndrome arise during therapy with QT interval–prolonging antiarrhythmics, as listed in Table 1. For some of these, such as quinidine and dofetilide, estimates of incidence range as high as 3–5%, although patients at especially high or low risk can be identified on clinical grounds (10). Treatment with drugs not intended for cardiovascular therapy has also been associated with drug-induced QT interval prolongation and arrhythmias, although the frequency of the problem appears to be much smaller. Nevertheless, because this rare adverse effect can be fatal, its recognition after the marketing of a drug can profoundly affect the perception of risk versus benefit that goes into the approval or prescription of the drug. Indeed, QT interval prolongation, with the potential for fatal arrhythmias, has been the single most common cause of withdrawal or relabeling of marketed drugs in the last decade (2); examples have occurred in multiple drug classes and include antihistamines (terfenadine and astemizole), gastrointestinal agents (cisapride), antipsychotics (sertindole), and urologic agents (terodiline).

Mechanisms underlying QT interval prolongation and torsade de pointes

First principles. QT interval prolongation on the surface ECG represents prolongation of action potentials in at least some regions of the ventricle (Figure 2). First principles in cellular electrophysiology dictate that such action potential prolongation, in turn, must reflect either a decrease in outward, repolarizing currents (flowing primarily through potassium channels) or an increase in plateau inward current (flowing primarily through calcium and sodium channels). Importantly, and as discussed further by Moss and Kass in an accompanying article in this series (11), mutations in genes encoding potassium, sodium, and calcium channels (as well as the structural protein ankyrin-B) have been linked to the congenital form of long QT syndrome, a disease with features — including torsade de pointes — in common with the acquired syndrome. As predicted, the potassium channel mutations result in decreased outward currents, and the calcium and sodium channel mutations result in increased plateau inward current.

HERG/I_{Kr} blockade. While mutations in any 1 of at least 8 genes can cause congenital QT interval prolongation, drugs that produce acquired long QT syndrome almost inevitably target a specific potassium current, the rapid component of the delayed rectifier, termed I_{Kr} (12). I_{Kr} is generated by expression of the human ether-à-go-go–related gene (*HERG*, also known as *KCNH2*), mutated in the LQT2 form of the congenital syndrome (13, 14). In heterologous systems, expression of *HERG* is sufficient to generate I_{Kr}; expression of other genes, such as *KCR1* (15) or *KCNE2* (16), generates proteins that appear to modulate I_{Kr} function in these systems, although their role in cardiomyocytes is less well established.

The very interesting question of why *HERG* channels are so readily blocked by a wide range of drugs to produce acquired long QT syndrome, while other potassium channels seem much less susceptible, has been addressed by Sanguinetti and colleagues (17–19) (Figure 3). A common drug-binding site in the channel is located on the intracellular face on the pore region, as in many other ion channels. Two key structural features inferred in the *HERG* pore, absent in other potassium channels, appear to underlie the "promiscuity"

Nonstandard abbreviations used: CAST, Cardiac Arrhythmia Suppression Trial; EAD, early afterdepolarization; *HERG*, human ether-à-go-go–related gene; I_{Kr}, the rapid component of the delayed rectifier; I_{Ks}, the slow component of the delayed rectifier.

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Table 1
Causes of acquired long QT syndrome

Drugs	
	Drugs that frequently cause torsade de pointes
	Disopyramide
	Dofetilide
	Ibutilide
	Procainamide
	Quinidine
	Sotalol
	Drugs clearly associated with torsade de pointes but with low incidence[A]
	Amiodarone
	Arsenic trioxide
	Erythromycin
	Droperidol
	Haloperidol
	Thioridazine
	Methadone
Heart block	
Hypokalemia, hypomagnesemia[B]	
Acute myocardial infarction[B]	
Subarachnoid hemorrhage and other CNS injury[B]	
Liquid protein diets and other forms of starvation[B]	

[A]There are case reports of torsade de pointes with many other drugs. Lists that give some sense of overall risk with a particular drug are maintained at http://www.torsades.org. [B]These are rare causes of torsade de pointes, but may increase risk when other causes are present.

of the channel's vulnerability to blockade by drugs. The first is the presence of multiple aromatic residues oriented to face the permeation pore; these provide high-affinity binding sites for a wide range of compounds. Other binding sites have been identified within the channel pore that may modulate on-and-off rates. The second key feature is absence of a pair of proline residues in the S6 helix that forms part of the pore. As a result, the S6 helix is not kinked in the *HERG* channel, and thus it is hypothesized that access to the binding site is less restricted than in other channels, allowing access to the blocking site by a wide range of drugs. Further understanding of drug binding might allow prediction of structures unlikely to bind to the channel, or structures that will unbind so quickly as to not produce the tonic blockade required to prolong QT intervals.

Why is potassium channel blockade arrhythmogenic? When preparations from the canine conduction system (Purkinje fibers) are exposed to conditions that promote torsade de pointes clinically (slow rates, low extracellular potassium, or drugs), action potentials not only lengthen but also develop distinctive morphologic abnormalities termed early afterdepolarizations (EADs) and triggered upstrokes (20–23) (Figure 4). These findings suggest that triggered upstrokes arising from EADs are 1 potential initiating mechanism for the arrhythmia. Importantly, EADs and triggered activity arise only indirectly from potassium channel inhibition; it seems likely that action potential prolongation by I_{Kr} blockade enables activation or reactivation of arrhythmogenic inward currents that underlie EADs and triggering. These may include calcium channels or the sodium-calcium exchanger (24, 25). Some studies also suggest a facilitatory role for intracellular calcium overload (26, 27), which would agree with the finding that heart failure appears to increase incidence of the arrhythmia (28, 29).

An increasingly well recognized feature of ventricular repolarization is that normal action potential durations and configurations vary across the ventricular wall (30, 31). It is this heterogeneity that results in a distinct positive T wave on the surface ECG (Figure 2). A key transmural difference is that action potential durations are longest in the midmyocardium (the "M cell" layer), and shorter in epicardial and endocardial regions. Two sets of experimental data, not necessarily mutually exclusive, have been advanced to explain this difference: M cells have been reported to display a decrease in a second, slow component of the delayed rectifier potassium current (32), termed I_{Ks}, as well as an increase in current flowing through sodium channels during the plateau ("late" sodium current) (33). The molecular basis for these changes has not been elucidated.

The effect of blocking I_{Kr} has been studied both in experimental systems in which all cell types are represented (such as the canine left ventricular perfused "wedge") and using computer models in which the effects of individual membrane currents on action potentials can be computed (34, 35). In both the in vitro and the in silico work, I_{Kr} blockade in M cells produces striking action potential prolongation, similar to that produced in Purkinje fibers, while epicardial and endocardial cells show much smaller changes (Figure 2). This exaggeration of physiologic heterogeneities of action potential duration in turn increases the susceptibility to transmural reentry, a likely mechanism underlying torsade de pointes (36, 37). Interestingly, this transmural dispersion mechanism has also been identified in congenital long QT syndrome, in other congenital diseases such as Brugada syndrome and the recently described short QT syndrome, and in heart failure (38–40). An important clinical implication of the recognition of the role of heterogeneity of repolarization in arrhythmia susceptibility has been that the measurement of the QT interval alone may not be an especially good guide to torsade de pointes risk. Instead, other indices of repolarization, such as T wave morphology or T peak and T end time, may be more sensitive indicators of this dispersion and hence the arrhythmogenic substrate (30, 31, 41, 42); however, these measures remain to be validated.

Animal models for the study of torsade de pointes. One animal model for the study of torsade de pointes is anesthetized rabbits, in which drugs producing the arrhythmia in patients regularly produce torsade de pointes but only if infused after pretreatment with the α-blocker methoxamine (43, 44). A second is dogs in which the atrioventricular node has been destroyed to create complete heart block (45, 46). After atrioventricular nodal ablation, QT intervals progressively prolong over weeks, and torsade de pointes is then readily induced by drug infusion. A likely mechanism in both situations is inhibition of I_{Ks} and perhaps other repolarizing currents to enhance the pharmacologic effect of I_{Kr} blockade. In the dog model, striking action potential lability on drug exposure separates arrhythmia-prone from arrhythmia-resistant animals (47), again suggesting that indices of repolarization beyond simple measurement of the QT interval may be useful in gauging risk.

Identifying patients at risk

Clinical features. The typical pause dependence of the arrhythmia is illustrated in Figure 1 (48–51). There also appears to be an increase in underlying heart rate before the onset of an episode of arrhythmia (52), suggesting a role for adrenergic activation. The arrhythmia is treated by withdrawal of offending agents, correction of hypokalemia to greater than 4–4.5 mEq/l (53), and empiric magnesium regardless of the serum magnesium (54); if the arrhythmia

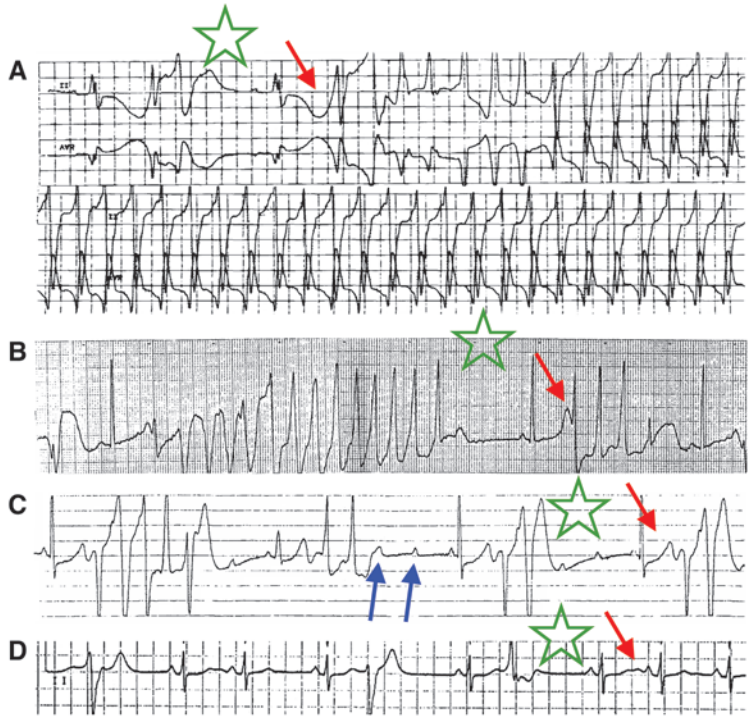

Figure 1
Examples of acquired long QT syndrome. A common feature is a pause (often after an ectopic beat), indicated by a star, with deranged repolarization in the following cycle (red arrows). (**A**) Continuous recording from a 79-year-old man with advanced heart disease treated with the antiarrhythmic dofetilide. The abnormal QT interval is followed by 7 beats of polymorphic ventricular tachycardia (torsade de pointes). In this patient, torsade de pointes then precipitated sustained monomorphic ventricular tachycardia, due to underlying heart disease. (**B**) Torsade de pointes in a patient treated with the antipsychotic haloperidol. (**C**) Torsade de pointes in a patient with complete heart block. The blue arrows indicate nonconducted atrial depolarizations. (**D**) Markedly abnormal postpause repolarization in a patient with advanced heart failure. Such disordered repolarization may represent increased risk for torsade de pointes (7).

recurs, temporary pacing or isoproterenol to prevent the pauses preceding the arrhythmia is used.

Over the past 2 decades, several clinical features have been consistently identified in multiple series of drug-induced torsade de pointes (48–51). These are listed in Table 2, and their identification at the clinical level has enabled interesting and important mechanistic research at the molecular level. For example, hypokalemia is a very common feature among patients with drug-induced torsade de pointes, and lowering of extracellular potassium decreases I_{Kr}, an effect that likely contributes to QT interval prolongation in hypokalemic patients (55, 56). However, this effect on I_{Kr} is unexpected, since simple electrochemical considerations predict an increase in outward potassium current with lowering of extracellular potassium. Two explanations have been advanced to explain this paradoxical behavior. One is that sodium and potassium compete for access to extracellular binding sites on the channel and sodium is a potent blocker of the current (57). As a result, when extracellular potassium is lowered, the inhibitory effect of sodium on the current becomes more apparent. The second explanation involves the very rapid inactivation that I_{Kr} undergoes after opening during depolarizing pulses (55). Lowering of extracellular potassium enhances this fast inactivation, so with hypokalemia more channels are in the inactivated state and fewer in the open state during depolarizing pulses. This very rapid inactivation also explains why the HERG channel, which generates I_{Kr}, plays such a key role in repolarization (Figure 2). During the plateau, most HERG channels are in the inactivated state. As repolarization is initiated at the beginning of phase 3 of the action potential, channels recover from inactivation and enter the open state before closing. Thus, as the action potential starts its repolarizing trajectory, I_{Kr} increases (reflecting more channels in the open state), thereby further accelerating repolarization. As discussed above, this is a major protective mechanism against arrhythmias, since it prevents the development of arrhythmogenic inward currents during the end of the action potential.

Another twist on hypokalemia as a risk factor has been the observation that drug blockade is actually enhanced at low levels of extracellular potassium (58, 59). Thus, hypokalemia potentiates

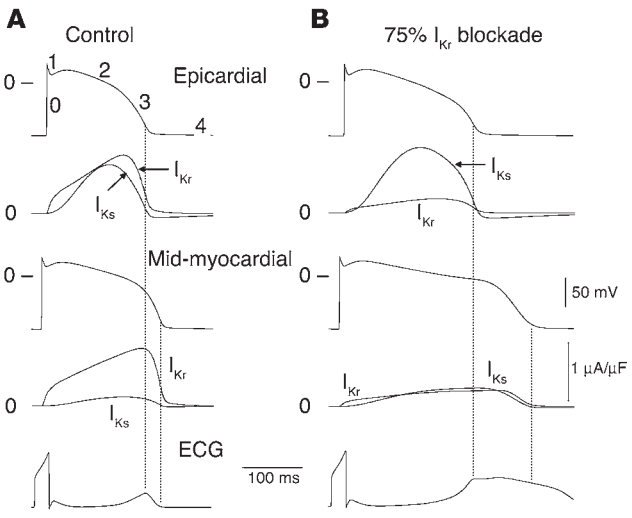

Figure 2
Computed action potentials, using the Luo-Rudy simulation (94) modified to include a transient outward current. This simulation incorporates physiologically realistic numerical models of individual ion currents and other electrogenic events (e.g., exchangers) and thereby allows in silico prediction of the effects of lesions in individual components on the whole physiologic system. **A** and **B** each show (from top to bottom) epicardial action potential, I_{Kr} and I_{Ks} during the epicardial action potential, midmyocardial action potential, I_{Kr} and I_{Ks} during the midmyocardial action potential, and an ECG signal computed from a 1-dimensional fiber consisting of endocardial, midmyocardial, and epicardial cells connected through resistive gap junctions (95). (**A**) Control. The numbered phases of the action potential are shown on the epicardial signal. Note the increase in I_{Kr} at the beginning of phase 3; as discussed in the text, this serves to enhance repolarization. The dotted lines indicate the ends of repolarization in the epicardial and midmyocardial cells and correspond roughly to the peak and end of the T wave, respectively. (**B**) 75% I_{Kr} blockade. Note that action potentials at both sites are prolonged, and the difference between them is exaggerated. The T wave abnormality in the computed ECG also reflects formation of EADs in endocardial cells (not shown).

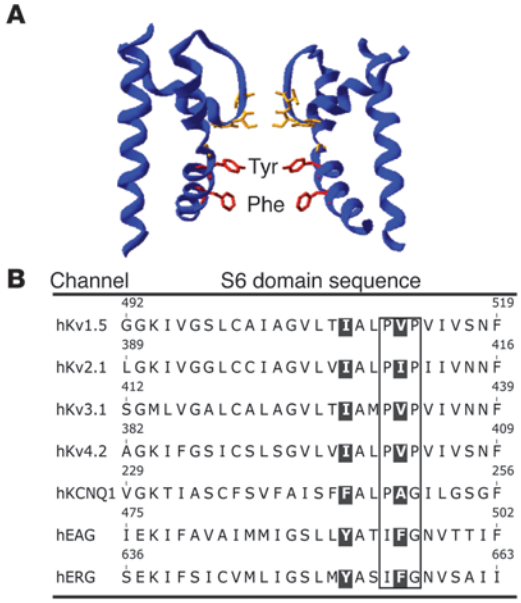

Figure 3
Hypothesized molecular structure of the drug-binding site in the HERG channel. (**A**) The orientation of the channel pore, lined by S6 helices, is shown; drug access is via the intracellular face of the channel. Portions of 2 of the 4 subunits of the homotetrameric channel are shown, and the other 2 are omitted for clarity. The aromatic residues (tyrosine [Tyr] and phenylalanine [Phe]) that face the pore are thought to be high-affinity drug-binding sites. (**B**) Sequence comparisons between HERG and other potassium channels. With the exception of the closely related hEAG channel, the others have 1 or 2 prolines in S6 and 0 or 1 aromatic residues. As discussed in the text, these 2 features appear to determine the ease with which the HERG channel is blocked by a wide range of drugs. Adapted with permission from the *Journal of Biological Chemistry* (19).

torsade de pointes risk through at least 2 mechanisms: (a) a decrease in the repolarizing current itself, and (b) potentiation of drug blockade of residual current. The mechanisms underlying other factors listed in Table 2, such as increased risk immediately following cardioversion of atrial fibrillation (60), have not yet been elucidated at the molecular level.

Reduced repolarization reserve. Figure 5 summarizes the way in which blockade of a single channel, encoded by *HERG*, can culminate in sudden death due to ventricular fibrillation; the key intermediate steps are action potential prolongation, EADs, QT interval prolongation, and torsade de pointes. A unifying framework for approaching these underlying mechanisms, and thereby understanding variability in response to HERG channel blockade and, in particular, why only very few patients exposed to HERG blockers die suddenly, has been the concept of reduced repolarization reserve (61). The starting point for this concept is that cardiac repolarization is determined by net outward current over time, itself a function not only of I_{Kr} and I_{Ks}, but also of other inward and outward currents during the plateau of the action potential. A defect in any 1 of these mechanisms may, therefore, remain subclinical if other pathways to normal repolarization are intact. The animal models discussed above are one example. Another is the phenomenon of "exposure" of subclinical congenital long QT syndrome due to mutations in the genes encoding I_{Ks} (62–64). Such cases suggest that mutations reducing this repolarizing current may be tolerated because of a robust I_{Kr}. However, administration of an I_{Kr}-blocking drug to such patients may then expose the defect in repolarization and result in marked QT interval prolongation and torsade de pointes (Figure 4). It seems likely that this framework can be used to analyze the role of other less well understood risk factors, such as female sex, heart failure, or left ventricular hypertrophy. In each, it seems likely that a subclinical defect in repolarization is exposed by inhibition of I_{Kr}. This framework is actually a specific example of the more general concept that systems controlling many physiologic processes, such as blood pressure, xenobiotic elimination, and protection from cancer, are usually highly redundant. A single lesion in such a system thus often remains clinically inapparent, and multiple lesions may be required to actually develop an overt phenotype, such as hypertension, an unusual drug reaction due to decreased clearance, or cancer.

Role of genetic variants in acquired long QT syndrome

QT interval prolongation, with the exception of that induced by quinidine, is increased at high plasma concentrations. Hence, genetic variants that impair elimination of an I_{Kr}-blocking drug may increase risk for torsade de pointes. The antipsychotic agent thioridazine is eliminated by the cytochrome P450 CYP2D6, which is functionally absent because of loss-of-function variants in the gene in approximately 7% of white and black individuals; the current FDA labeling warns of increased torsade de pointes risk with thioridazine in the poor-metabolizer group.

Subclinical long QT syndrome. The identification of congenital long QT syndrome disease genes has led to screening of large kindreds, and the recognition of incomplete penetrance, i.e., mutation carriers with normal ECGs. The identification of such individuals after an episode of torsade de pointes argues that mutations not generating baseline QT interval prolongation may nevertheless still con-

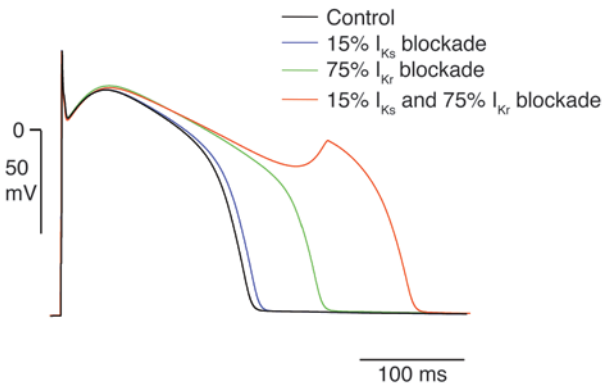

Figure 4
Luo-Rudy simulations showing the concept of repolarization reserve. The blue line shows the effect of reducing I_{Ks} by 15%, as might be expected in a subtle congenital long QT syndrome mutation. The green line shows the expected prolongation of the control action potential resulting from 75% I_{Kr} blockade. The red line shows the effect of the same degree of drug blockade applied to the simulation with 15% I_{Ks} blockade. Not only is there marked exaggeration of action potential prolongation, but an EAD with a triggered upstroke is also generated; L-type calcium current generates the upstroke in this model.

Table 2
Risk factors for torsade de pointes in the presence of a culprit drug[A]

Female sex
Hypokalemia
Hypomagnesemia
Bradycardia
Heart failure
Recent conversion from atrial fibrillation
Ion channel variants
Subclinical or unrecognized congenital long QT syndrome
Polymorphisms in congenital long QT syndrome disease genes
Other polymorphisms
High drug concentrations[B]
Left ventricular hypertrophy
Rapid i.v. drug bolus

[A]Evidence for most of these is derived from nonrandomized case series and/or studies in animal models. [B]Quinidine is an exception.

fer risk on drug exposure. Analyses of probands with drug-induced long QT syndrome have identified the subclinical congenital syndrome in a minority (less than 10%); mutations have been reported in *KCNQ1*, encoding the pore-forming subunit underlying I_{Ks}; *HERG* itself; the K^+ channel subunit genes *KCNE1* and *KCNE2*; and *SCN5A*, encoding the cardiac sodium channel (64, 65).

Polymorphisms in congenital long QT syndrome disease genes. These analyses have also identified polymorphisms in long QT syndrome ion channel genes, some of which may be overrepresented in patients with drug-induced or other arrhythmias. One striking example is S1103Y in the cardiac sodium channel gene (66). When 23 black patients with a range of arrhythmias, including drug-induced long QT syndrome, were compared with black controls, this variant was overrepresented in the patients, with a minor allele frequency of 13%. In vitro studies identified a subtle gating defect that increased the risk of EADs with I_{Kr} blockade in computed (in silico) action potentials. The S1103Y variant has not been identified in other ethnic groups, except for a single report in a white family, in which it was implicated as the disease-causing mutation in manifest congenital long QT syndrome (67). These studies point to the increasingly well-recognized role of ethnicity in polymorphism frequencies and in modulation of important physiologic and drug-response phenotypes (68). Thus, any study examining the genetic determinants of these endpoints must include a consideration of ethnicity.

Another lesson in this regard was the *KCNE2* variant, which results in Q9E. This was initially described as a mutation in a black woman with drug-induced long QT syndrome, because it was absent in more than 1,000 normal controls. However, this turns out to be a relatively common polymorphism, occurring in 3.2% of black people (69). Other rare polymorphisms with minor allele frequencies of 1–2% that have been implicated in drug-induced torsade de pointes include D85N (KCNE1) and T8A (KCNE2) (65, 70, 71).

Extending the list of candidate variants. These studies identified DNA variants — mutations and polymorphisms — associated with drug-induced long QT syndrome by testing the hypothesis that variants in the congenital long QT syndrome disease genes might contribute to risk in the drug-induced form. Patients with the target phenotype (drug-induced torsade de pointes) were screened for variants in these genes; the frequency of these variants was then determined in control populations, and the function of the variants was determined by in vitro heterologous expression of variant ion channels. An alternate paradigm may now be emerging, driven both by an increasing appreciation of the large number of genes that determine normal cardiac electrophysiology, and by improvements in high-throughput genetic technologies. Rather than confining the list of candidate genes to those with mutations causing congenital arrhythmia syndromes, the alternate approach generates a list of many dozens or more based on a current understanding of normal cardiac electrophysiology. High-throughput screening of these genes is then undertaken to identify common or functionally important polymorphisms, and their frequency is then compared in patients with the target phenotype and controls. Using this approach, we have identified I447V in *KCR1* as a potential modulator of the risk of drug-induced torsade de pointes; the valine variant occurred in 1.1% of patients, compared with 7% in controls, suggesting that the presence of valine in this position protects against drug-induced torsade de pointes (15).

Genome science and arrhythmia phenotypes. While this new approach appears to be an appealing way of integrating contemporary genomics into arrhythmia science, there are a number of obstacles. The first is the very large number of candidate genes and the correspondingly huge number of polymorphisms that have already been described in these candidates. The second is the problem of false positives, highlighted by reports that most association studies are not reproducible (72, 73). One way to bolster an association between a genetic variant and a clinical phenotype is to describe modified biology conferred by the variant that could explain the phenotype. Thus, the argument that a coding region polymorphism in an ion channel gene contributes to variability in an arrhythmia phenotype can be bolstered by demonstration that the polymorphism produces altered channel function. In addition, it is possible to then use computer simulations (e.g., Figures 2 and 4) to predict how such variant channel function might modify action potentials and arrhythmia susceptibility (35, 66, 70, 74). In this way, an association

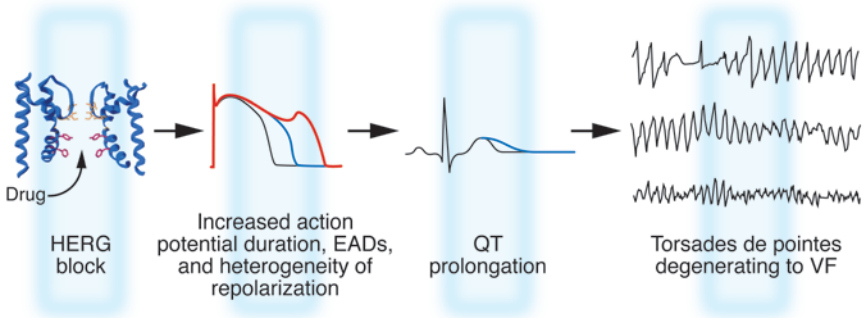

Figure 5
Mechanisms of sudden death with HERG blockade. Drug blockade of the HERG channel (left) produces prolongation (blue) and an EAD (red) in the cardiac action potential. These changes, which are heterogeneous across the ventricular wall, generate QT interval prolongation and, through mechanisms described further in the text, torsade de pointes (right; upper panel). In this example, the arrhythmia degenerates to ventricular fibrillation (VF).

study is supported by an argument of biological plausibility. Unfortunately, in many instances, methods have not yet been developed to demonstrate that a DNA variant alters function or expression of the encoded protein, or that such changes alter the behavior of a complex system like the action potential.

Although there are millions of single-nucleotide and other polymorphisms in the human genome, it is apparent that large haplotype blocks display high linkage disequilibrium (75). Therefore, the number of polymorphisms to be analyzed in an association paradigm can be reduced by study of "haplotype tagging" polymorphisms. Indeed, a common haplotype blockade in the cardiac sodium channel — a key determinant of conduction velocity in the heart — has been associated with variability in the QRS duration (an index of conduction velocity in the ventricle) in a normal population (76). This haplotype blockade is in a noncoding region that includes the core promoter, and so the effect, if reproduced, seems likely attributable to variable sodium channel transcription as a contributor to interindividual variability in conduction velocity. As with the problem of predicting QT changes caused by a drug in an individual patient, the consequences of such differences may be minimal among healthy subjects but may variably engender important differences among individuals — in this case in the critically slow conduction that underlies many forms of reentry — on exposure to further stressors, such as sodium channel–blocking drugs and/or ischemia. Thus, it is even conceivable that the adverse effects of sodium channel blockers (including increased mortality due to arrhythmias, demonstrated by the Cardiac Arrhythmia Suppression Trial [CAST; ref. 77]) might reflect, in part, such genetically determined variable susceptibility to arrhythmias.

Implications for development of new drugs

Lessons learned after high-profile drug withdrawals, notably of terfenadine and cisapride, have important implications for development of new drugs. Both agents were developed before the molecular details of torsade de pointes outlined above were known. Although both turn out to be potent I_{Kr} blockers, torsade de pointes was actually quite rare, because both drugs undergo near-complete presystemic biotransformation to noncardioactive metabolites by members of the CYP3A family of cytochrome P450s (78–80); another key pharmacokinetic feature that the drugs share is that they lack robust alternate elimination mechanisms. It was largely in patients with impairment of this presystemic metabolism — due to overdose, liver disease, or concomitant therapy with potent CYP3A inhibitors such as ketoconazole or erythromycin — that the drugs accumulated in the systemic circulation and caused torsade de pointes.

Erythromycin itself is another example of a drug that may cause torsade de pointes rarely. Erythromycin is a weak I_{Kr} blocker that is also metabolized by CYP3A; the drug has been reported to cause torsade de pointes when used i.v. at high doses (81), and recent pharmacoepidemiologic data suggest that coadministration of oral erythromycin with CYP3A inhibitors increases sudden death rate, compared with a control antibiotic (ampicillin) or erythromycin used alone (82). These data reinforce the notion that rare but serious risks with drugs can go unappreciated for years unless specifically sought because of in vitro studies or clinical case reports.

The lessons learned by understanding of the mechanisms in these cases have broad applicability. Because virtually all drugs that cause torsade de pointes act by blocking the *HERG* channel, it has become standard practice to screen new drug candidates for this activity prior to clinical trials. However, because the channel is so readily blocked, many candidates blockade *HERG* channels, so a common question is whether this property is important for a potential new drug's safety profile (83–85). To answer this question requires several other pieces of information. The first is the potency of I_{Kr} blockade compared with that of activity at the target molecular site of action; the smaller the margin between the two, the more likely that HERG blockade could occur at clinically relevant doses. A second is the disposition kinetics of the drug: is it likely that some patients could generate very high plasma concentrations (of parent drug, or perhaps of active metabolites) that would place them at high risk? Such aberrant drug responses can arise because of drug interactions or because of a genetically based absence of a pathway for drug elimination. In either case, a marker of a high-risk situation is the presence of only a single pathway for drug elimination. A third piece of information is whether the drug candidate exerts other electrophysiologic effects that could potentiate, or blunt, action potential prolongation and thus torsade de pointes risk. Amiodarone and verapamil both block I_{Kr}; however, amiodarone causes torsade de pointes only rarely (86), while verapamil has actually been used to treat the arrhythmia (87). The drugs' effects on other channels, notably inward current via calcium channels, likely blunt action potential prolongation and afterdepolarizations due to I_{Kr} blockade. The antianginal agent ranolazine similarly blocks I_{Kr} but does not produce an arrhythmogenic phenotype in the wedge preparation; this has been attributed to blockade of plateau sodium current (88). Further clinical experience will be required to assess the clinical effects of this agent. Finally, a risk for torsade de pointes may be acceptable for a serious medical condition for which alternate therapies are not available and for which treatment in monitored conditions or for short periods of time is the norm; by contrast, even a tiny risk might be unacceptable for a drug being developed for long-term outpatient therapy of a nuisance symptom, and for which other therapies are available. Data attesting to the lack of torsade de pointes in pre-marketing clinical trials, which generally include no more than several thousand patients, cannot rule out serious risk, as the terfenadine, cisapride, and erythromycin examples show. Screening for HERG activity has presented a major headache for the pharmaceutical industry but has correspondingly reduced the likelihood that new drugs will unexpectedly cause torsade de pointes.

Other acquired arrhythmia syndromes

The concept that analysis of monogenic disease genes can be used as a starting point for analysis of more common clinical phenotypes can be extended from the long QT syndromes to other arrhythmias. Brugada syndrome is due to loss-of-function mutations in *SCN5A* in approximately 20% of patients (89). Some of these patients have a manifest electrocardiographic phenotype, while in others the baseline ECG is normal and the ECG changes typical of the syndrome are only exposed by challenge with a sodium channel–blocking drug. Taken together, the results of these Brugada syndrome studies and of the CAST point to loss of sodium channel function as a potential contributor to an arrhythmia-prone substrate. Thus, patients who take sodium channel–blocking drugs or have subclinical reduction-of-function *SCN5A* variants may be entirely asymptomatic until a further insult that reduces sodium channel function (e.g., transient myocardial ischemia) occurs, increasing their risk of fatal ventricular fibrillation.

The logic extends to very common arrhythmia phenotypes. Sudden cardiac death due to ventricular fibrillation affects 400,000–500,000 Americans each year, is the cause of death in more than 25% of adults, and is the first symptom of heart disease in over 50% of victims. Analyses from a number of databases indicate that a family history of sudden cardiac death increases risk in the proband; this suggests that genetic factors contribute to risk (90, 91). One obvious candidate gene is *SCN5A*, but many others could be inferred based on an increasingly sophisticated understanding of cardiac myocyte physiology. Similarly, atrial fibrillation affects millions of Americans and is generally thought to be a disease of aging. However, atrial fibrillation can occur in youth and midlife, and in these situations it is generally unassociated with any other disease (lone atrial fibrillation) or associated with hypertension, which is often mild. As with sudden death, family studies support a role for a genetic contributor to risk (92, 93). Therefore, atrial fibrillation may in fact be largely a genetic disease, but with incomplete penetrance; i.e., a genetic predisposition combined with as-yet unidentified environmental factors may be sufficient to elicit the arrhythmia in susceptible individuals.

Conclusions

Studies of both rare and common arrhythmias are thus converging on a common model in which genetic makeup interacts with environmental stressors to generate specific clinical phenotypes. In some cases, the phenotype may be manifest without additional provokers. The best examples are patients with monogenic arrhythmia syndromes such as congenital long QT syndrome, or full-blown Brugada syndrome. At the other end of this spectrum are common phenotypes such as sudden death and atrial fibrillation. Studies of drug-induced long QT syndrome can thus be viewed not simply as an interesting exercise in understanding a relatively uncommon adverse drug interaction, but as laying the foundation for a new paradigm in understanding the role of genetic factors in mediating common arrhythmia phenotypes.

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