Torsade de pointes (TdP) is a life-threatening arrhythmia that develops as a consequence of a reduction in the repolarization reserve of cardiac cells leading to amplification of electrical heterogeneities in the ventricular myocardium as well as to the development of early afterdepolarization-induced triggered activity. Electrical heterogeneities within the ventricles are due to differences in the time course of repolarization of the three predominant cell types that make up the ventricular myocardium, giving rise to transmural voltage gradients and a dispersion of repolarization that contributes to the inscription of the electrocardiographic T wave. A number of non-antiarrhythmic drugs and antiarrhythmic agents with class III actions and/or the various mutations and cardiomyopathies associated with the long QT syndrome reduce net repolarizing current and amplify spatial dispersion of repolarization, thus creating the substrate for re-entry. This results in a prolongation of the QT interval, abnormal T waves, and development of TdP. Agents that prolong the QT interval but do not cause an increase in transmural dispersion of repolarization (TDR) do not induce TdP, suggesting that QT prolongation is not the sole or optimal determinant for arrhythmogenesis. This article reviews recent advances in our understanding of these mechanisms, particularly the role of TDR in the genesis of drug-induced TdP, and examines how these may guide us towards development of safer drugs.

**KEYWORDS**
LQTS; TdP; Electrophysiology; Sudden cardiac death; Transmural dispersion of repolarization; Arrhythmia

**Introduction**
Drug or disease-mediated reduction in net repolarizing current of cardiac cells can lead to prolongation of the QT interval and in some cases to the development of life-threatening cardiac arrhythmias. A number of non-antiarrhythmic drugs and antiarrhythmic agents with class III actions and the various mutations and cardiomyopathies associated with the long QT syndrome (LQTS) reduce net repolarizing current and amplify spatial dispersion of repolarization, thus creating the substrate for re-entry. This results in a prolongation of the QT interval, abnormal T waves, and development of polymorphic ventricular tachycardia, known as torsade de pointes (TdP). Some agents and syndromes prolong the QT interval but do not cause an increase in transmural dispersion of repolarization (TDR). These agents and conditions generally do not induce TdP, suggesting that QT prolongation is not the sole determinant for the development of arrhythmias. This article reviews recent advances in our understanding of the mechanisms involved in the development of TdP, particularly the role of spatial dispersion of repolarization, with the goal of providing us some guidance in the development of safer and more effective drugs.

**Electrical heterogeneities in ventricular myocardium**
In that, the inscription of the T wave is due to electrical heterogeneities within the ventricular myocardium and the substrate for arrhythmogenesis attending the LQTS develops as a consequence of amplification of these spatial heterogeneities, it may be appropriate to begin with a description of the cellular and ionic distinctions that normally exist within the ventricles of the heart.

It is now well established that ventricular myocardium is composed of at least three electrophysiologically and functionally distinct cell types: epicardial, mid-myocardial (M), and endocardial cells. These three principal ventricular myocardial cell types differ with respect to phase 1 and phase 3 repolarization characteristics. Ventricular epicardial and M, but not endocardial, cells generally display a prominent phase 1, due to a large 4-aminopyridine sensitive transient outward current (I\text{to}), giving the action potential a spike and dome or notched configuration. These regional differences in I\text{to} have now been directly demonstrated in canine, feline, rabbit, rat, and human ventricular myocytes. Differences in the magnitude of the action potential notch and corresponding differences in I\text{to} have also been described between right and left ventricular epicardial and M cells. This distinction is thought to form the basis for why the Brugada syndrome,
a channelopathy-mediated form of sudden death, is a right ventricular disease.

Separating the surface epicardial and endocardial layers are transitional and M cells. M cells are distinguished by the ability of their action potential to prolong disproportionately relative to the action potential of other ventricular myocardial cells in response to a slowing of rate and/or in response to action potential duration (APD)-prolonging agents.\(^{1,4,15}\) In the dog, the ionic basis for these features of the M cell include the presence of a smaller slowly activating delayed rectifier current (\(I_{Kr}\)), a larger late sodium current (\(I_{Na}\)), and a larger Na-Ca exchange current (\(I_{Na-Ca}\)).\(^{1,8}\) In the canine heart, the rapidly activating delayed rectifier (\(I_{K1}\)) and inward rectifier (\(I_{Kr}\)) currents are similar in the three transmural cell types (Figure 1). Transmural and apico-basal differences in the density of \(I_{Ks}\) channels have been described in the ferret heart.\(^{13}\) \(I_{Ks}\) mRNA and channel protein are much larger in the ferret epicardium. \(I_{Kr}\) is larger in M cells isolated from the right vs. left ventricles of the dog.\(^{13}\)

Calcium channel current (\(I_{Ca}\)) has been shown to be similar among cells isolated from epicardium, \(M\), and endocardial regions of the left ventricular wall.\(^{20,21}\) One study, however, reported differences in Ca\(^{2+}\) channel properties between epicardial and endocardial canine ventricular cells. In that study, \(I_{Ca}\) was found to be larger in endocardial than in epicardial myocytes (3.4 ± 0.2 vs. 2.3 ± 0.1 pA/pF). A low threshold, rapidly activating, and inactivating Ca\(^{2+}\) current that resembled the T-type current was also recorded in all endocardial myocytes, but was small or absent in epicardial myocytes. The T-like current was composed of two components: an \(I_{Kr}\)/-sensitive T-type current and a tetrodotoxin-sensitive Ca\(^{2+}\) current.\(^{22}\)

Histologically, M cells are similar to epicardial and endocardial cells. Electrophysiologically and pharmacologically, they appear to be a hybrid between Purkinje and ventricular cells.\(^{23}\) Like Purkinje fibres, M cells show a prominent APD prolongation and develop early afterdepolarizations (EAD) in response to \(I_{Ks}\) blockers, whereas epicardium and endocardium do not. Like Purkinje fibres, M cells develop delayed afterdepolarizations in response to agents that calcium load or overload the cardiac cell; epicardium and endocardium do not. Unlike Purkinje fibres, M cells display an APD prolongation in response to \(I_{Kr}\) blockers; epicardium and endocardium also show an increase in APD in response to \(I_{Ks}\) blockers. Purkinje and M cells also respond differently to \(\alpha\)-adrenergic agonists. \(\alpha_1\)-adrenoceptor stimulation produces APD prolongation in Purkinje fibres, but abbreviation in M cells, and little or no change in endocardium and epicardium.\(^{24}\)

The distribution of M cells within the ventricular wall has been investigated in greatest detail in the left ventricle of the canine heart. Although transitional cells are found throughout the wall in the canine left ventricle, M cells displaying the longest action potentials [at basic cycle lengths (BCLs)>2000 ms] are often localized in the deep subendocardium to mid-myocardium in the anterior wall,\(^{25}\) deep subepicardium to mid-myocardium in the lateral wall,\(^{14}\) and throughout the wall in the region of the right ventricular outflow tracts.\(^{26}\) M cells are also present in the deep cell layers of endocardial structures, including papillary muscles, trabeculae, and the interventricular septum.\(^{26}\) Unlike Purkinje fibres, M cells are not found in discrete bundles or islets,\(^{26,27}\) although there is evidence that they may be localized in discrete muscle layers. Cells with the characteristics of M cells have been described in the canine, guinea pig, rabbit, pig, and human ventricles.\(^{6,14-16,25-45}\)

### Transmural dispersion of repolarization and inscription of the electrocardiographic T wave

Transmural and apico-basal heterogeneities of final repolarization of the action potential within ventricular myocardium are thought to be responsible for inscription of the T wave.\(^{43,46}\) Studies involving the arterially perfused wedge have shown that currents flowing down voltage gradients on either side of the M region are in a large part responsible for the T wave.\(^{43}\) The interplay between these opposing forces establishes the height and width of the T wave and the degree to which either the ascending or the descending limb of the T wave is interrupted, leading to a bifurcated or notched appearance (Figure 2).\(^{43}\) The voltage gradients result from a more positive plateau potential in the M region than in epicardium or in endocardium, as well as from differences in the time course of phase 3 of the action potential of the three predominant ventricular cell types.

Under normal and most long QT conditions, the epicardial response is the earliest to repolarize and the M cell action potential is often the last. Full repolarization of the epicardial action potential is coincident with the peak of the T wave and repolarization of the M cells coincides with the end of the T wave. Thus, the repolarization of the M cells of the heart usually determines the QT interval. The interval between the peak and end of the T wave (\(T_{peak}\)–\(T_{end}\)) has been suggested to provide an index of TDR, which may be of prognostic value for proarrhythmic risk.\(^{43,47}\)

Apico-basal repolarization gradients measured along the epicardial surface have been suggested to play a prominent role in the registration of the T wave.\(^{36,46}\) However, studies involving the perfused wedge suggest little or no contribution.\(^{43}\)

### The long QT syndromes

Prolongation of the QT interval, the time interval between ventricular depolarization and repolarization, on the surface electrocardiogram (ECG) is caused by an increase in the APD of ventricular myocytes. Prolongation of the QT interval can occur as a consequence of congenital defects in, or in response to drugs that prolong the APD via a reduction in \(I_{Ks}\), \(I_{K1}\), or \(I_{Kr}\); or an increase in \(I_{Ca}\) or late \(I_{Na}\). The inherited forms of the LQTSs are phenotypically and genotypically diverse, but have in common the appearance of a long QT interval in the ECG, an atypical polymorphic ventricular tachycardia known as TdP, and, in many but not all cases, a relatively high risk for sudden cardiac death.\(^{49-51}\) Congenital LQTS is subdivided into 10 genotypes distinguished by mutations in at least seven different ion channel genes and a gene encoding a structural anchoring protein.\(^{52-60}\) Two patterns of inheritance have been identified: a rare autosomal recessive disease associated with deafness (Jervell and Lange-Nielsen), caused by two genes that encode for the slowly activating delayed rectifier potassium channel (\(KCNQ1\) and \(KCNE1\)); and a much more...
Figure 1 Ionic distinctions among epicardial (Epi), mid-myocardial (M), and endocardial (Endo) cells. (A) Action potentials recorded from myocytes isolated from the epicardial, endocardial, and M regions of the canine left ventricle.© 1993 Lippincott Williams & Wilkins, reprinted with permission. (B) I-V relations for $I_{K1}$ in epicardial, endocardial, and M region myocytes. Values are mean ± SD. (C) Transient outward current ($I_{to}$) recorded from the three cell types (current traces recorded during depolarizing steps from a holding potential of $-80 \text{ mV}$ to test potentials ranging between $-20$ and $+70 \text{ mV}$).© 1993 Lippincott Williams & Wilkins, reprinted with permission. (D) The average peak current–voltage relationship for $I_{to}$ for each of the three cell types.© 1993 Lippincott Williams & Wilkins, reprinted with permission. (E) Voltage-dependent activation of the slowly activating component of the delayed rectifier $K^+$ current ($I_{Ks}$) (currents were elicited by the voltage pulse protocol shown in the inset; Na$^+$-, K$^+$-, and Ca$^{2+}$-free solution).© 1995 Lippincott Williams & Wilkins, reprinted with permission. (F) Voltage dependence of $I_{Ks}$ (current remaining after exposure to E-4031) and $I_{Kr}$ (E-4031-sensitive current).© 1995 Lippincott Williams & Wilkins, reprinted with permission. (G) Reverse-mode sodium–calcium exchange currents recorded in potassium- and chloride-free solutions at a voltage of $-80 \text{ mV}$. $I_{Na-Ca}$ was maximally activated by switching to sodium-free external solution at the time indicated by the arrow. (H) Mid-mycocardial sodium–calcium exchanger density is 30% greater than endocardial density, calculated as the peak outward $I_{Na-Ca}$ normalized by cell capacitance. Endocardial and epicardial densities were not significantly different.© 2000 American Physiological Society, reprinted with permission. (I) Tetrodotoxin-sensitive late $I_{Na}$. Cells were held at $-80 \text{ mV}$ and briefly pulsed to $-45 \text{ mV}$ to inactivate fast sodium current before stepping to $-10 \text{ mV}$. (J) Normalized late sodium current measured 300 ms into the test pulse was plotted as a function of test pulse potential.
common autosomal dominant form known as the Romano-Ward syndrome, caused by mutations in 10 different genes, including KCNQ1 (KvLQT1; LQT1), KCNH2 (HERG; LQT2), SCN5A (Na\(_{\text{v}}\),1.5; LQT3), ANK8 (LQT4), KCNE1 (minK; LQT5), KCNE2 (MIRP1; LQT6), KCNJ2 (LQT7; Andersen’s syndrome), CACNA1C (Ca\(_{\text{v}}\),1.2; LQT8; Timothy syndrome), CAV3 (Caveolin-3; LQT9), and SCN4B (Na\(_{\text{v}}\)B4; LQT10). Six of the 10 genes encode for cardiac potassium channels, one for the cardiac sodium channel (SCN5A), one for the β subunit of the sodium channel, one for caveolin-3, and one for a protein called ankyrin B (ANKB), which is involved in anchoring of ion channels to the cellular membrane.

The prevalence of this disorder is estimated at 1–2:10 000. The ECG diagnosis is based on the presence of prolonged repolarization (QT interval) and abnormal T-wave morphology.\(^{61}\) In the different genotypes, cardiac events may be precipitated by physical or emotional stress (LQT1), a startle (LQT2), or may occur at rest or during sleep (LQT3). Anti-adrenergic intervention with β-blockers is the mainstay of therapy. For patients unresponsive to this approach, implantable cardioverter defibrillator and/or cardiac sympathetic denervation may be therapeutic alternatives.\(^{62,63}\)

Acquired LQTS refers to a syndrome similar to the congenital form but caused by exposure to drugs that prolong the duration of the ventricular action potential\(^{64}\) or QT prolongation secondary to cardiomyopathies such as dilated or hypertrophic cardiomyopathy, as well as to abnormal QT prolongation associated with bradycardia or electrolyte imbalance.\(^{65–69}\) Most of the drugs that cause acquired LQTS block \(I_{\text{Kr}}\), many also block \(I_{\text{Ks}}\), and some augment late \(I_{\text{Na}}\), so that in many ways they are similar to congenital forms of LQTS. The acquired form of the disease is far more prevalent than the congenital form, and may have a genetic predisposition.

Amplification of spatial dispersion of repolarization within the ventricular myocardium has been identified as the principal arrhythmogenic substrate in both acquired and congenital LQTS. The accentuation of spatial dispersion, typically secondary to an increase of transmural, septal or apico-basal dispersion of repolarization, and the development of EAD-induced triggered activity underlie the substrate and trigger for the development of Tdp arrhythmias observed under LQTS conditions.\(^{70,71}\) Models of the LQT1, LQT2, LQT3, and LQT7 forms of the LQTS have been developed using the canine arterially perfused left ventricular wedge preparation (Figure 3).\(^{72–74}\) These models suggest that in the first three forms of LQTS, preferential prolongation of the M cell APD can lead to an increase in the QT interval as well as an increase in TDR, which contributes to the development of spontaneous as well as stimulation-induced Tdp (Figure 4).\(^{36,41,75}\)

The unique characteristics of the M cells are at the heart of the LQTS. The hallmark of the M cell is the ability of its action potential to prolong more than that of epicardium or endocardium in response to a slowing of rate.\(^{4,14,76}\) As previously detailed, this feature of the M cell is due to weaker repolarizing current during phases 2 and 3 secondary to a smaller \(I_{\text{Ko}}\) and a larger late \(I_{\text{Na}}\) and \(I_{\text{Na–Ca}}\) compared with epicardial and endocardial cells.

These ionic distinctions sensitize the M cells to a variety of pharmacological agents and pathophysiological states. Agents that block \(I_{\text{Ko}}, I_{\text{Ks}}\) or increase \(I_{\text{Ca}}\) or late \(I_{\text{Na}}\) generally
produce a much greater prolongation of the APD of the M cell than of epicardial or endocardial cells (Figure 3).

Experimental models that mimic the clinical congenital syndromes with respect to prolongation of the QT interval, T-wave morphology, and rate dependence of QT have also been helpful in elucidating the basis for sympathetic nervous system influences (Figure 3).25,36,41–43

\( I_{Ks} \) block using chromanol 293B is used to mimic LQT1. \( I_{Ks} \) block alone produces a homogeneous prolongation of repolarization and refractoriness across the ventricular
of TdP in the model requires long QT interval characteristics of LQT1. The development of TdP in the LQT1 (TdP\textsubscript{41}) gives rise to a broad-based T wave and the development of spontaneous and stimulation-induced TdP. The addition of hypokalaemia gives rise to low-amplitude T waves with a deeply notched or bifurcated appearance, similar to those commonly seen in patients with the LQT2 syndrome.\textsuperscript{36,41} Isoproterenol further exaggerates TDR, thus increasing the incidence of TdP.\textsuperscript{75}

ATX-II, an agent that increases late $I_{\text{Na}}$, is used to mimic LQT3.\textsuperscript{36} ATX-II markedly prolongs the QT interval, delays the onset of the T wave, in some cases also widening it, and produces a sharp rise in TDR as a result of a greater prolongation of the APD of the M cell. The differential effect of ATX-II to prolong the M cell action potential is likely due to the presence of a larger late $I_{\text{Na}}$ in the M cell.\textsuperscript{17} ATX-II produces a marked delay in onset of the T wave because of a relatively large effect of the drug on epicardial and endocardial APD. This feature is consistent with the late-appearing T wave (long isoelectric ST segment) observed in patients with the LQT3 syndrome. Also in agreement with the clinical presentation of LQT3, the model displays a steep rate dependence of the QT interval and develops TdP at slow rates. Interestingly, $\beta$-adrenergic influence in the form of isoproterenol reduces TDR by abbreviating the APD of the M cell more than that of epicardium or endocardium, and thus reducing the incidence of TdP. Although the $\beta$-adrenergic blocker propranolol is protective in LQT1- and LQT2-wedge models, it has the opposite effects in LQT3, acting to amplify transmural dispersion and promoting TdP.\textsuperscript{75}

It is interesting that the response to sympathetic activation displays a very different time course in the case of LQT1 and LQT2, both in experimental models (Figure 3) and in the clinic.\textsuperscript{71,79} In LQT1, $\beta$-adrenergic stimulation induces an increase in TDR that is most prominent during the first 2 min, but which persists, although to a lesser extent, during steady state. TdP incidence is enhanced during the initial period as well as during steady state. In LQT2, isoproterenol produces only a transient increase in TDR that persists for $<2$ min. TdP incidence is therefore enhanced only for a brief period of time. These differences in time course may explain the important differences in autonomic activity and other gene-specific triggers that contribute to events in patients with different LQTS genotypes.\textsuperscript{75,78,80}

Although $\beta$-blockers are considered the first line of therapy in patients with LQT1, they have not been shown to be beneficial in LQT3. Preliminary data suggest LQT3 patients might benefit from Na\textsuperscript{+}-channel blockers, such as mexiletine and flecainide, but long-term data are not yet available.\textsuperscript{81,82} Experimental data have shown that mexiletine reduces transmural dispersion and prevents TdP in LQT3 as well as in LQT1 and LQT2, suggesting that agents that block the late $I_{\text{Na}}$ may be effective in all forms of LQTS.\textsuperscript{36,41} These observations suggest that a combination of $\beta$-blockers and late sodium channel blockers may confer more protection in LQT1 and LQT2 than $\beta$ blockade alone. The anti-anginal ranolazine, a potent blocker of late $I_{\text{Na}}$, consistent with the high sensitivity of congenital LQTS, LQT1 in particular, to sympathetic stimulation,\textsuperscript{56–51,77,78}

wall and does not induce arrhythmias. The addition of isoproterenol causes abbreviation of epicardial and endocardial APD but a prolongation or no change in the APD of the M cell, resulting in a marked augmentation of TDR and the development of spontaneous and stimulation-induced TdP.\textsuperscript{41} These changes give rise to a broad-based T wave and the long QT interval characteristics of LQT1. The development of TdP in the model requires $\beta$-adrenergic stimulation,
has been shown to be very effective in suppressing TdP in experimental models of LQTS1, LQTS2, and LQTS3. Clinical data are not available as yet.

$T_{\text{peak}} - T_{\text{end}}$ interval as an index of transmural dispersion of repolarization

In the wedge preparation, $T_{\text{peak}} - T_{\text{end}}$ interval has been shown to provide a measure of TDR. In the intact heart, such equivalency is not to be expected, yet we hypothesize that $T_{\text{peak}} - T_{\text{end}}$ may provide an important non-invasive index of changes in spatial dispersion of repolarization, particularly TDR. The available data suggest that $T_{\text{peak}} - T_{\text{end}}$ measurements might best be limited to precordial leads (V1–V6) since these leads more accurately reflect TDR. Recent studies have provided guidelines for the estimation of TDR in the case of more complex T waves, including negative, biphasic, and triphasic T waves. With these complexes, the interval from the nadir of the first component of the T wave to the end of the T wave provides an accurate electrocardiographic approximation of TDR.

Although the clinical applicability of these concepts remains to be carefully validated, significant progress towards validation of the $T_{\text{peak}} - T_{\text{end}}$ interval as an index of transmural dispersion has been advanced. Lubinski et al. demonstrated that this interval is increased in patients with congenital LQTS. Recent studies suggest that the $T_{\text{peak}} - T_{\text{end}}$ interval may be a useful index of transmural dispersion and thus may be prognostic of arrhythmic risk under a variety of conditions. Takenaka et al. recently demonstrated exercise-induced accentuation of the $T_{\text{peak}} - T_{\text{end}}$ interval in LQT1 patients, but not LQT2. These observations coupled with those of Schwartz et al. demonstrating an association between exercise and risk for TdP in LQT1, but not LQT2, patients, once again point to the potential value of $T_{\text{peak}} - T_{\text{end}}$ in forecasting risk for TdP in patients with LQTS. Shimizu et al. demonstrated that $T_{\text{peak}} - T_{\text{end}}$, but not QTc, predicted sudden cardiac death in patients with hypertrophic cardiomyopathy. Most recently, Watanabe et al. demonstrated that prolonged $T_{\text{peak}} - T_{\text{end}}$ is associated with inductability as well as spontaneous development of ventricular tachycardia in high-risk patients with organic heart disease. Although additional studies are clearly needed to evaluate the utility of these non-invasive indices of electrical heterogeneity and their prognostic value in the assignment of arrhythmic risk, evidence is accumulating in support of the hypothesis that TDR rather than QT prolongation underlies the substrate responsible for the development of TdP.

Figure 5 presents a working hypothesis for our understanding of the mechanisms underlying LQTS-related TdP based on available data. The hypothesis assumes the presence of electrical heterogeneity in the form of transmural or transseptal dispersion of repolarization under baseline conditions and the amplification of TDR by agents that reduce net repolarizing current via a reduction in $I_{\text{Kr}}$ or $I_{\text{ks}}$ or augmentation of $I_{\text{ca}}$ or late $I_{\text{Na}}$. Conditions that cause a reduction in $I_{\text{Kr}}$ or augmentation of late $I_{\text{Na}}$ lead to a preferential prolongation of the M cell action potential. As a consequence, the QT interval prolongs and is accompanied by a dramatic increase in TDR, thus creating a vulnerable window for the development of re-entry. The reduction in net repolarizing current also predisposes to the development of EAD-induced triggered activity in M and Purkinje cells, which provide the extrasyntole that triggers TdP when it falls within the vulnerable period. β-adrenergic agonists further amplify transmural heterogeneity (transiently) in the case of $I_{\text{Kr}}$ block, but reduce it in the case of $I_{\text{Na}}$ agonists.

Although many agents and conditions that prolong QT are associated with an increase in TDR, this is not always the case. Amiodarone, a potent antiarrhythmic agent used in the management of both atrial and ventricular arrhythmias, is rarely associated with TdP. Chronic administration of amiodarone produces a greater prolongation of APD in epicardium and endocardium, but less of an increase in APD, or even a decrease at slow rates, in the M region, thereby reducing TDR. Sodium pentobarbital is another agent that prolongs the QT interval but reduces TDR. Pentobarbital has been shown to produce a dose-dependent prolongation of the QT interval, accompanied by a reduction in TDR from 51 to 27 ms. TdP is not observed under these conditions, nor can it be induced with programmed stimulation. Amiodarone and pentobarbital have in common the ability to block $I_{\text{Na}}$, $I_{\text{Kr}}$, and late $I_{\text{Na}}$. This combination produces a preferential prolongation of the APD of epicardium and endocardium so that the QT interval is prolonged, but TDR is actually reduced and TdP does not occur.

Cisapride is another agent that blocks both inward and outward currents. Cisapride produces a biphasic concentration-dependent prolongation of the QT interval (Figure 6). A parallel biphasic dose–response relationship is seen for TDR, peaking at 0.2 μM, and it is only at this concentration that TdP is observed. Higher concentrations of cisapride further prolonged QT, but reduced TDR, thereby reducing TDR.
thereby preventing TdP induction.97 This finding suggests that the spatial dispersion of repolarization is more important than the prolongation of the QT interval in determining the substrate for TdP.

Chromanol 293B, an IKs blocker, is another example of an agent that increases QT without augmenting TDR. Chromanol 293B prolongs APD of the three cell types homogeneously, neither increasing TDR nor widening the T wave (Figure 7). Torsade de pointes is not observed under these conditions. Although an arrhythmogenic substrate is not present with IKs block alone, it develops very quickly with the introduction of β-adrenergic stimulation. Isoproterenol abbreviates the APD of epicardial and endocardial cells but not that of the M cell, resulting in a marked accentuation of TDR.75 Torsade de pointes readily develops under these conditions.

These observations have advanced our understanding of why long-QT patients, LQT1 in particular, are so sensitive to sympathetic influences, and have provided further evidence in support of the hypothesis that the risks associated with LQTS are not due to the prolongation of the QT interval but rather to an increase in spatial dispersion of repolarization that usually, but not always, accompanies the prolongation of the QT interval.

Figure 8 summarizes the effects of the different QT prolonging agents. In the first example, pure IKr blockers such as sotalol, dofetilide, and erythromycin produce a dose-dependent prolongation of the QT interval that is associated with a dose-dependent prolongation of TDR. When TDR reaches the threshold for re-entry, which in the canine wedge preparation is ~90 ms, TdP will occur.
With more complex agents such as quinidine and cisapride, there is a biphasic dose–response relationship. TDR parallels QT, but the two can peak at different concentrations. Torsade de pointes occurs when, and if, TDR reaches the threshold value. Other drugs produce a dose-dependent prolongation of QT, but a smaller increase or even a decrease in TDR; threshold values for TdP are rarely reached. Finally, agents that preferentially block $I_{Kr}$, such as chromanol 293B, and agents with multiple ion channel effects, including pentobarbital, amiodarone, and the new anti-anginal agent ranolazine, produce a dose-dependent prolongation of QT but a much smaller change in transmural dispersion of repolarization; here, threshold values for torsade de pointes are rarely reached. Torsade de pointes is never observed with drugs that prolong QT but produce a dose-dependent reduction in transmural dispersion of repolarization. TdP, torsade de pointes; TDR, transmural dispersion of repolarization. © 2005 Elsevier Inc., reprinted with permission.

Collectively, these observations clearly indicate that prolongation of the ventricular action potential or QT interval is not the sole determinant of the potential of a drug to cause TdP. QT prolongation is a relatively mediocre predictor of TdP when it comes to evaluation of drug action. Some drugs can cause a large QT prolongation, but, by reducing TDR, may actually reduce the likelihood of TdP. Other electrophysiological markers need to be developed in order to more accurately assign clinical risk. TDR, represented by $T_{peak}$–$T_{end}$, may provide a more accurate electrophysiological marker of risk than the QT interval. Use of this marker will require a great deal of prospective validation, both in in vivo models and in the clinic.

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