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Heterogeneity of cellular repolarization in LQTS: the role of M cells

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QT prolongation, whether congenital or acquired, is commonly associated with life-threatening torsade de pointes (TdP) arrhythmias that develop as a consequence of the amplification of electrical heterogeneities intrinsic to the ventricular myocardium. Electrophysiologic distinctions among the three predominant cell types that comprise the ventricular myocardium are responsible for the normal dispersion of repolarization and transmural voltage gradients that inscribe the J and T waves of the ECG. Differences in the response of epicardial, endocardial and M cells to pharmacologic agents and/or pathophysiological states result in amplification of these intrinsic electrical heterogeneities, thus providing a substrate and trigger for the development of reentrant arrhythmias. Transmural dispersion of repolarization secondary to disproportionate prolongation of the action potential of M cells in response to a reduction in net repolarizing current often leads to the development of a vulnerable window, long QT intervals, abnormal T waves as well as to the induction of polymorphic VT resembling torsade de pointes. The decrease in net repolarizing current also predisposes M cells and Purkinje fibres to develop early afterdepolarization-induced triggered activity, which is responsible for the generation of extrasystoles thought to precipitate TdP. Agents that prolong the QT interval but do not increase transmural dispersion of repolarization are not capable of inducing TdP. Thus, the available data suggest that that the principal problem with the long QT syndrome is not long QT intervals, but rather the dispersion of repolarization that often accompanies prolongation of the QT interval.

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Key Words: Long QT syndrome, transmural dispersion, repolarization abnormalities, T wave, U wave.

Introduction

Drug-induced QT prolongation is commonly associated with life-threatening torsade de pointes (TdP) arrhythmias that develop as a consequence of the amplification of electrical heterogeneities intrinsic to the ventricular myocardium. This review describes the heterogeneity of ventricular repolarization present under normal and pathophysiological conditions and the cellular mechanisms that contribute to arrhythmogenesis accompanying QT prolongation.

The past decade has witnessed a transition in our thinking of ventricular myocardium from a homogeneous entity to one that is rich in its cellular diversity. Numerous studies have highlighted regional differences in electrical properties of ventricular cells as well as differences in the response of the diverse cell types to pharmacological agents and pathophysiological states (for review see References [1–4]). Among the heterogeneities uncovered are electrical and pharmacological distinctions between endocardium and epicardium of the canine, feline, rabbit, rat and human heart as well as differences in the electrophysiological characteristics and pharmacological responsiveness of M cells located in the deep structures of the canine, rabbit, pig, guinea-pig and human ventricles.

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Cellular and ionic basis for the heterogeneous repolarization of ventricular myocardium

Studies published over the past decade have established that ventricular myocardium is comprised of at least three electrophysiologically distinct cell types: epicardial, M and endocardial. The three ventricular myocardial cell types differ principally with respect to phase 1 and phase 3 repolarization characteristics (Fig. 1A). Ventricular epicardial and M, but not endocardial, cells display a conspicuous phase 1, due to a prominent 4-aminopyridine (4-AP) sensitive transient outward current (I_{to}), giving the action potential a spike and dome or notched configuration. These regional

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differences in I_{to}, first suggested on the basis of action potential data, have now been demonstrated using whole cell patch-clamp techniques in canine, feline, rabbit, rat and human ventricular myocytes (see Reference [4] for further references). Major differences in the magnitude of the action potential notch and corresponding differences in I_{to} have also been described between right and left ventricular epicardium[5] and left and right ventricular M cells[6].

Transmural and interventricular differences in I_{to} measurements have a number of interesting consequences, including: (1) the creation of a transmural gradient in the manifestation of the action potential notch, which is responsible for the inscription of the J wave; (2) differential sensitivity to ischaemia and components of ischaemia; (3) differential sensitivity to drugs such as (a) neurohormones (acetylcholine and isoproterenol), (b) transient outward current blockers, (c) calcium channel blockers, (d) sodium channel blockers, and (e) potassium channel openers[4].

M cells are distinguished by the ability of their action potential to prolong disproportionately, relative to the action potential of other ventricular myocardial cell types, in response to a slowing of rate and/or in response to drugs with QT prolonging actions[7–9]. The ionic basis for these features include the presence of a smaller slowly activating delayed rectifier current (I_{Ks})[10], a larger late sodium current (late I_{Na})[11] and a larger electrogenic sodium–calcium exchange current ($I_{Na\text{-}Ca}$)[12] (Fig. 1). The rapidly activating delayed rectifier (I_{Kr}) and inward rectifier (I_{Kl}) currents are similar in the three transmural cell types. Transmural and apico-basal differences in the density of I_{Kr} channels have been described in the ferret heart but not in the dog or human heart[13].

M cells are similar to epicardial and endocardial cells histologically, but electrophysiologically and pharmacologically, they appear to be a hybrid between Purkinje and ventricular cells (Table 1). M cells displaying the longest action potentials are often localized in the deep subendocardium to midmyocardium in the anterior wall[14], deep subepicardium to midmyocardium in the lateral wall[7] and throughout the wall in the region of the right ventricular (RV) outflow tracts[2]. M cells are also present in papillary muscles, trabeculae and the interventricular septum[15]. Unlike Purkinje fibres, they are not found in discrete bundles or islets[15,16]. Figure 2 illustrates the transmural distribution of APD_{90} and tissue resistivity in the canine left ventricle (LV). M cells with the longest action potentials are found in the deep subendocardium and transitions in action potential duration are relatively gradual across the ventricular wall, except in the region of the deep subepicardium where a sharp increase in tissue resistivity is observed[14]. The sharp increase in tissue resistivity between the M region and epicardium, which appears to be due in part to a sharp transition in cell orientation, is responsible for the sharp increase in APD in this region of the wall. A similar sharp re-orientation of cell direction is also observed in the deep subepicardium of the human LV, where prolonged M cell action potentials are first encountered[17].

Cells with M cell characteristics have been described in the canine, guinea-pig, rabbit, pig and human ventricles[7,9,10,14–34]. One of the earliest studies to infer delayed repolarization in the deep layers of the canine LV was that by Burgess *et al.*[35] in which repolarization was estimated by local measurement of refractoriness. Three studies involving pig, guinea-pig and rat have failed to discern M cells in the ventricles of the heart[25,36,37]. Two studies in the dog, while clearly showing the presence of M cells in the ventricles of the heart in vitro, failed to delineate the unique cell type in vivo[3,9]. The methodological problems responsible for these failures to observe the M cell are detailed elsewhere[4,38]. Among the factors involved are the use of (1) relatively fast stimulation rates, (2) bipolar recording techniques to estimate ARI or (3) sodium pentobarbital or alpha-chloralose anaesthesia, or a combination of these. Sodium pentobarbital, largely through its actions to block I_{Na} and I_{Ks}, reduces transmural dispersion of repolarization under baseline conditions and greatly suppresses the action of agents like d-sotalol and ATX-II to amplify transmural heterogeneity[30,39]. Another anaesthetic, alpha-chloralose, has been shown to exert a similar influence on transmural dispersion of repolarization. These findings urge caution in the interpretation of the results of in vivo studies performed with these and perhaps other anaesthetics. Concordant with these reports, the development of in vivo models of TdP has met with failure when sodium pentobarbital was used for anaesthesia[22] whereas TdP could be readily induced when halothane or isoflurane was employed[22,27,40,41] or when no anaesthesia is used[42,43].

Amplification of intrinsic heterogeneities

Intrinsic transmural heterogeneities of early repolarization are amplified by a wide variety of drugs and pathophysiological states that augment net repolarizing current during the early phases of the action potential. The enhanced phase 1, action potential notch and/or depressed action potential plateau in epicardium are responsible for the exaggeration of the electrocardiographic J wave and ST-segment elevation, which can lead to the development of ventricular tachycardia and fibrillation. The Brugada syndrome and other syndromes associated with ST-segment elevation can be unmasked or exacerbated by such agents, including vagomimetics and sodium channel blockers[4,44–48].

Intrinsic transmural heterogeneities of final repolarization can be dramatically amplified by drugs and pathophysiological states that reduce the repolarization forces within the heart. A hallmark of the M cell is the ability of its action potential to prolong more in response to agents with class III actions or APD prolonging effects (Fig. 3). I_{Kr} blockers, including d-sotalol,

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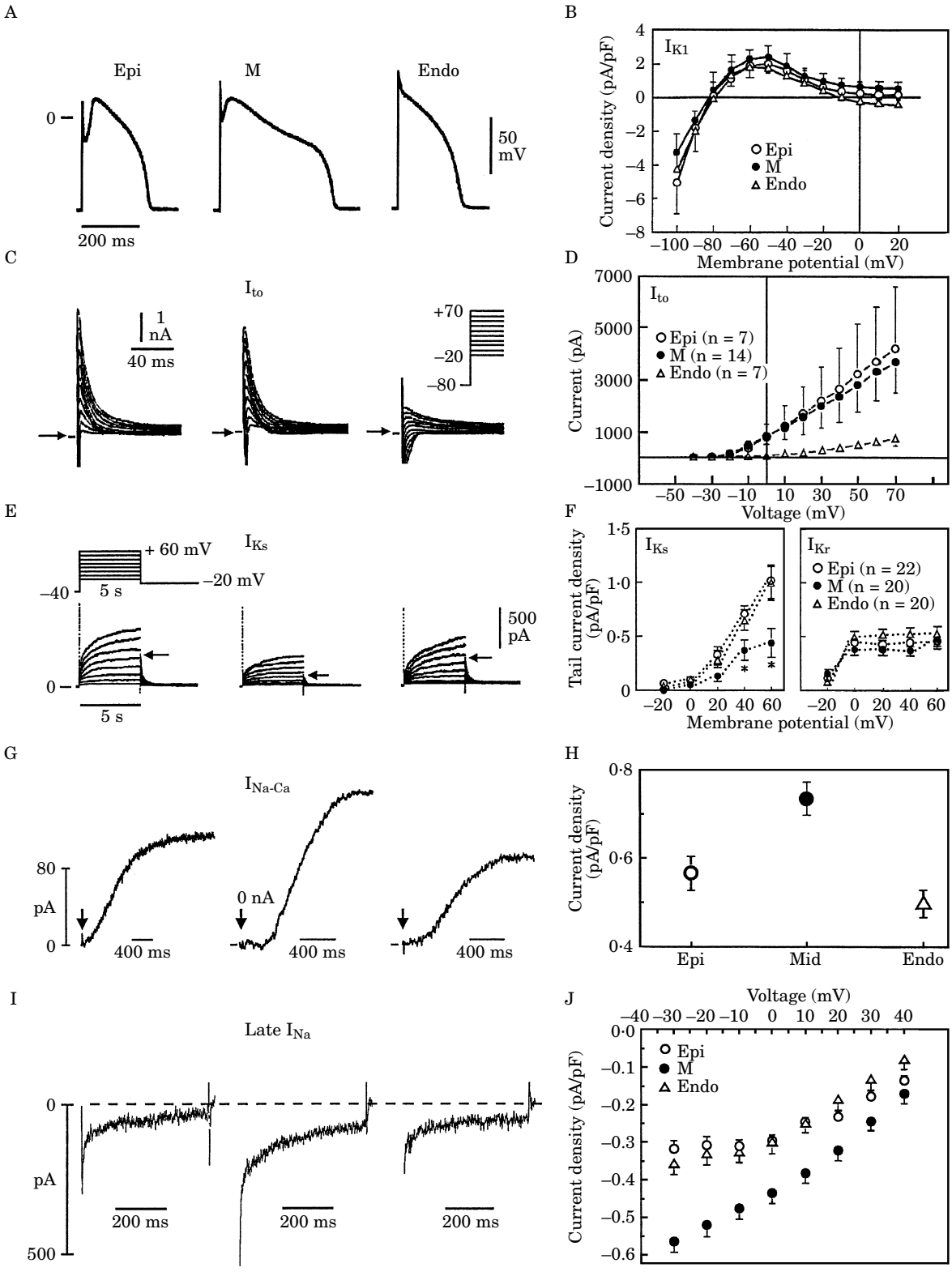

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Table 1

	Purkinje	M	Epicardial	Endocardial
Long APD, steep APD-rate	Yes	Yes	No	No
Develop EADs in response to agents with class III actions	Yes	Yes	No	No
Develop DADs in response to digitalis, high Ca^{2+}, catecholamines	Yes	Yes	No	No
Display marked increase in APD in response to I_{Kr} blockers	Yes	Yes	No	No
Display marked increase in APD in response to I_{Ks} blockers	No	Yes	No	No
α1 Agonist-induced change in APD	↑	↓	↔	↔
V_{max}	High	Intermediate	Low in surface tissues	
Phase 4 depolarization	Yes	No	No	No
Depolarization in $[K^+]_o < 2{\cdot}5$ mM	Yes	No	No	No
Acceleration-induced EADs and APD prolongation in presence of I_{Kr} block	No	Yes	No	No
EADs sensitive to $[Ca^{2+}]_I$	No	Yes	—	—
Found in bundles	Yes	No	No	No

ADP = action potential duration, EAD = early afterdepolarization;
DAD = delayed afterdepolarization.

almokalant, E-4031 and erythromycin, produce a much greater prolongation of APD in M cells than in epicardium or endocardium (Fig. 3, Table 2). Surface epicardial and endocardial tissues isolated from the canine LV show a much smaller response. A similar preferential prolongation of the M cell APD is seen with agents that increase calcium current, I_{Ca}, such as Bay K 8644 as well as with agents that augment late I_{Na} such as ATX-II and anthopleurin-A. An exception to this rule applies to agents that block I_{Ks}, including azimilide, quinidine, pentobarbital, amiodarone and chromanol 293B. Chromanol 293B is the most specific of the I_{Ks}

Figure 1 **A: Action potentials recorded from myocytes isolated from the epicardial, endocardial and M regions of the canine left ventricle. B: Current-voltage relationships for I_{Kl} 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 mV to test potentials ranging between −20 and +70 mV D: The average peak current-voltage relationship for I_{to} for each of the three cell types. Values are mean ± SD 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). F: Voltage dependence of I_{Ks} (current remaining after exposure to E-4031) and I_{Kr} (E-4031-sensitive current). Values are mean ± SE. *$P<0{\cdot}05$ compared with ePi or endo. (Reproduced with permission[10,12,20].) G: Reverse-mode sodium–calcium exchange currents recorded in potassium- and chloride-free solutions at a voltage of −80 mV. $I_{Na\text{-}Ca}$ was maximally activated by switching to sodium-free external solution at the time indicated by the arrow. H: Midmyocardial sodium–calcium exchanger density is 30% greater than endocardial density, calculated as the peak outward $I_{Na\text{-}Ca}$ normalized by cell capacitance. Endocardial and epicardial densities were not significantly different. I: TTX-sensitive late sodium current. Cells were held at −80 mV and briefly pulsed to −45 mV to inactivate fast sodium current before stepping to −10 mV. J: Normalized late sodium current measured 300 ms into the test pulse was plotted as a function of test pulse potential. (Modified with permission[12].)**

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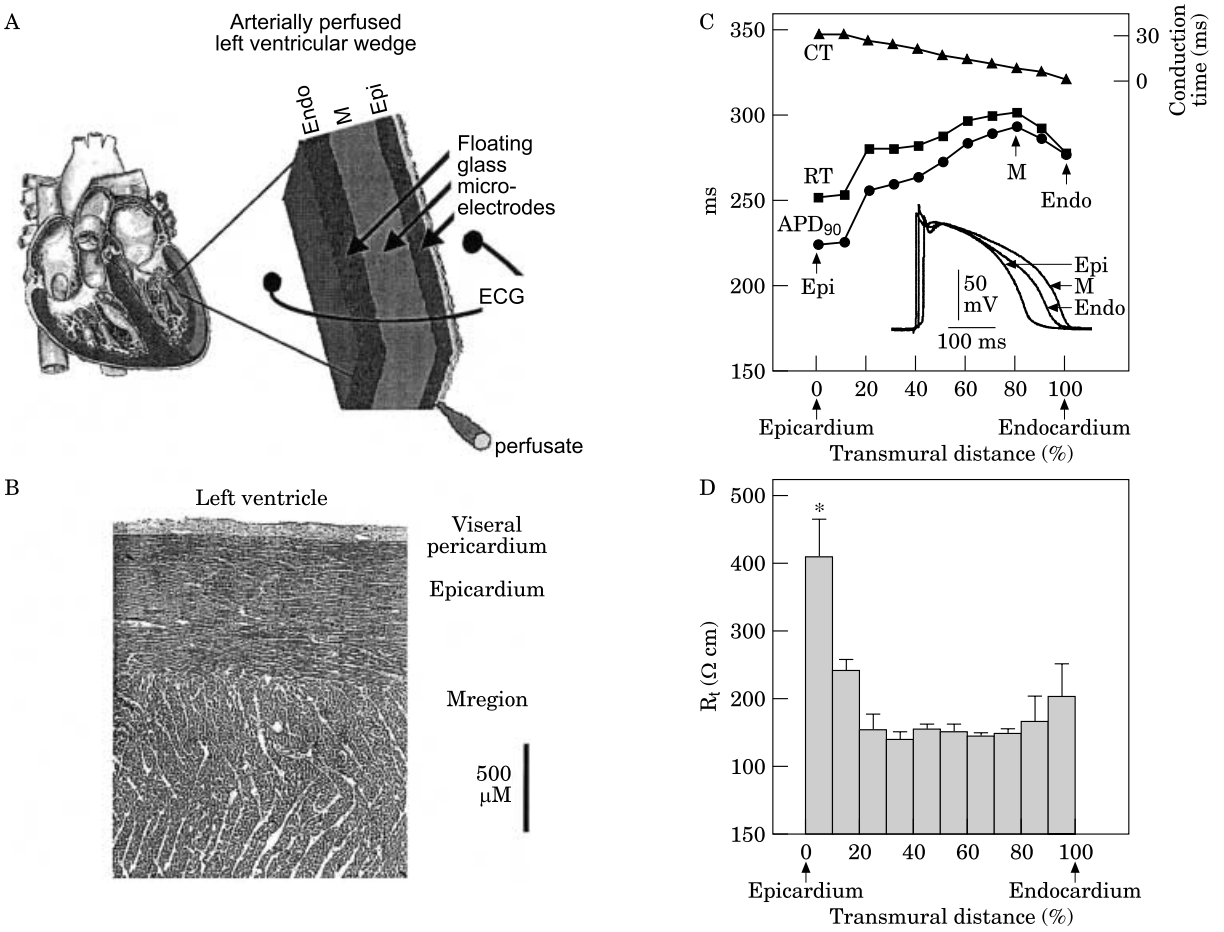

Figure 2 **Transmural distribution of action potential duration and tissue resistivity in the intact ventricular wall. A: Schematic diagram of the arterially perfused canine LV wedge preparation. The wedge is perfused with Tyrode's solution via a small native branch of the left descending coronary artery and stimulated from the endocardial surface. Transmembrane action potentials are recorded simultaneously from epicardial (Epi), M region (M) and endocardial (Endo) sites using three floating microelectrodes. A transmural ECG is recorded along the same transmural axis across the bath, registering the entire field of the wedge. B: Histology of a transmural slice of the left ventricular wall near the epicardial border. The region of sharp transition of cell orientation coincides with the region of high tissue resistivity depicted in panel D and the region of sharp transition of action potential duration illustrated in panel C. C: Distribution of conduction time (CT), APD_{90} and repolarization time ($RT = APD_{90} + CT$) in a canine left ventricular wall wedge preparation paced at BCL of 2000 ms. A sharp transition of APD_{90} is present between epicardium and subepicardium. Epi: epicardium; M: M Cell; Endo: endocardium. RT: repolarization time; CT: conduction time. D: Distribution of total tissue resistivity (R_t) across the canine left ventricular wall. Transmural distances at 0% and 100% represent epicardium and endocardium, respectively. *$P<0{\cdot}01$ compared with R_t at mid-wall. Tissue resistivity increases most dramatically between deep subepicardium and epicardium. Error bars represent SEM (n=5). (Reproduced with permission[14].)**

blockers. In isolated tissues, chromanol 293B produces a similar prolongation of APD (percentage-wise) in the three transmural cell types. The situation is more complex for drugs affecting two or more ion channels, such as quinidine, amiodarone, pentobarbital and azimilide (Fig. 4). In the case of quinidine, relatively low therapeutic levels of the drug (3–5 μM; 1·14–1·89 μg . ml^{-1}), produce a marked prolongation of the M cell APD but not the APD of epicardium and endocardium, consistent with a predominant effect of quinidine to block I_{Kr} at this concentration[39,49]. Higher concentrations of quinidine (10–30 μM; 3·78–11·37 μg . ml^{-1} produce a further prolongation of the epicardial and endocardial action potential, consistent with an effect of the drug to block I_{Ks}, and abbreviate the APD of the M cell, due to inhibition of late I_{Na}[50]. Voltage clamp studies have shown that low concentrations of quinidine potently block I_{Kr}, but not I_{Ks}, whereas higher concentrations potently block both I_{Kr} and I_{Ks}[38]. These multiple actions of quinidine have been suggested to underlie the ability of the drug to induce TdP at low therapeutic levels, but not at high therapeutic or toxic levels[38].

Drug-induced amplification of heterogeneities of final repolarization clearly is a result of differences in response of the diverse cell types to the ion channel

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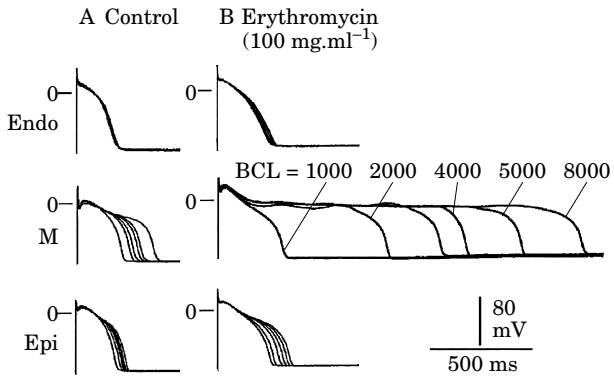

Figure 3 **Effects of a specific I_{Kr} blocker, erythromycin, on transmembrane activity recorded from epicardial (Epi), endocardial (Endo) and deep subepicardial (M cell) sites in a transmural strip of canine left ventricle. Each panel shows superimposed action potentials recorded at basic cycle lengths (BCL) of 1000–8000 ms. A: Control. B: Recorded after 30 min of exposure to l00 µg . ml^{-1} erythromycin. (Modified with permission[65].)**

effects of the drug. Table 3 illustrates the sensitivity of different canine ventricular cell types to four different ion channel manipulations known to prolong the QT interval and to induce TdP. This table indicates that, in the canine ventricle, only cells or tissue from the M region are capable of clearly identifying drugs representative of all four categories.

Physiological and clinical implications

Transmural dispersion of the I_{to}-mediated action potential notch

Transmural dispersion of early repolarization (I_{to}-mediated phase I) gives rise to a transmural distribution of the action potential notch, which is in large part responsible for the inscription of the electrocardiographic J wave. Differences in the response of the three cell types to pharmacological agents and/or pathophysiological states can result in amplification of these intrinsic electrical heterogeneities, thus providing a substrate as well as a trigger for the development of reentrant arrhythmias, including polymorphic VT/VF, in patients with the Brugada syndrome. Accentuation of the RV action potential notch is thought to be responsible for the development of a downsloping ST-segment elevation (or accentuation of the J wave) in Brugada patients. Further accentuation of the notch leads to an all-or-none repolarization of the RV epicardial action potential resulting in marked abbreviation of action potential duration (APD) at some right ventricular sites but not others. This results in the development of a transmural as well as epicardial dispersion of repolarization. Heterogeneous repolarization of the epicardial action potential gives rise to phase 2 re-entry, which provides an extrasystole capable of precipitating VT/VF (or rapid TdP)[44,46,51,52].

Table 3

Ion channel manipulation	Cell types: Purkinje	M	Endo	Epi
I_{Kr} block	↑↑↑	↑↑↑	◂▸↑	◂▸↑
I_{Ks} block	◂▸	↑↑	↑↑	↑↑
Activation of late I_{Na}	↑↑↑↑	↑↑↑↑	↑↑	↑↑
Activation of I_{Ca}	↑↑↑	↑↑↑	◂▸↑	◂▸↑

Table 2 Prominent action potential prolongation andlor early after-depolarization (EAD)-induced triggered activity

Drug treatment	Epicardium	Endocardium	M cells
Quinidine (3·3 µM)	−	−	+++
4-Aminopyridine (2·5–5 mM)	−	−	+++
Amiloride (1–10 µM)	−	−	++
Clofilium (1 µM)	−	−	+++
Bay K 8644 (1· µM)	−	−	++
Caesium (5–10 mM)	−	−	++
Sotalol (100 µM)	−	−	+++
Erythromycin (10–100 µg . ml^{-1})	−	−	++++
E-4031 (1–5 µM)	−	−	+++
Chronic amiodarone	+	−	++
ATX-II (10–20 nM)	+	++	++++
Azimilide (5–20 µM)	+	++	+++
Chromanol 293B (30–100 µM)	+++	+++	+++

+/− Little to no response; ++++greatest response.

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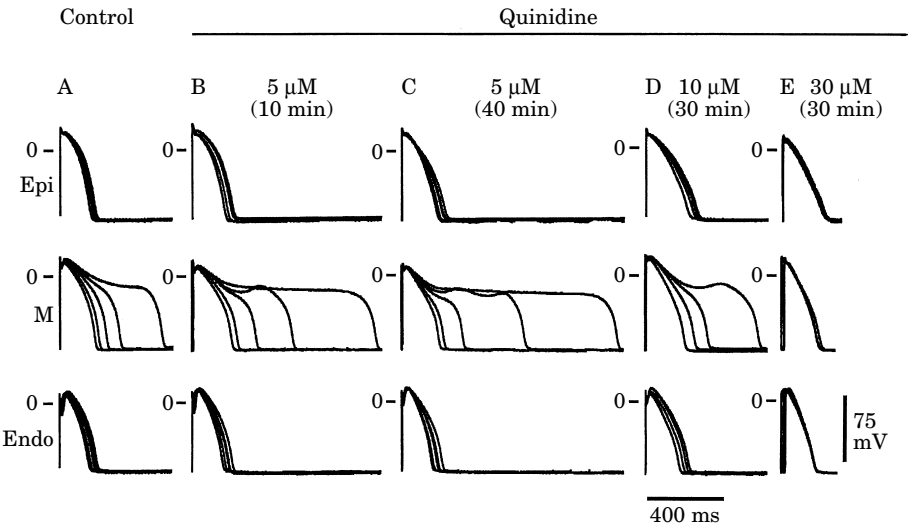

Figure 4 **Effect of 5, 10, and 30 μM quinidine on action potential activity in tissue slices isolated from the endocardial, M and endocardial regions of the canine ventricular free wall. Preparations were field stimulated at basic cycle lengths (BCLs) of 300, 500, 1000, 2000, 5000 and 8000 ms. A: Control, B: Recorded 10 min after addition of 5 μM quinidine; the M cell APD is preferentially prolonged. C: After 40 min of 5 μM, Epi, M and Endo APD further prolonged. D: 30 min of 10 μM quinidine caused an abbreviation of the M cell action potential but further prolongation of Epi and Endo. E: Recorded after 30 min of 30 μM. (Reproduced with permission[38].)**

Of note, the electrocardiographic manifestations of the Brugada syndrome are similar to those encountered during ischaemia. As such, the Brugada syndrome may represent a stable (non-ischaemic) model of the cellular changes that occur during acute ischaemic injury as well as of other syndromes associated with ST-segment elevation. The presence of an additional outward current (i.e. I_{to}) in ventricular epicardium predisposes to loss of the action dome during ischaemia, thus leading to amplification of transmural heterogeneities and the development of phase 2 re-entry and VT/VF.

Transmural heterogeneity of final repolarization and the electrocardiographic T wave

Under baseline conditions, M cells play the determining role in the inscription of the electrocardiographic T wave. Data from the arterially perfused wedge have provided new insights into the cellular basis of the T wave showing that currents flowing down voltage gradients on either side of the M region are in large part responsible for the T wave (Figs 5 and 6)[33]. The interplay between these opposing currents determines the height and width of the T wave as well as the degree to which the ascending or descending limb of the T wave is interrupted, leading to a bifurcated or notched appearance. The voltage gradients result from more positive plateau potentials in the M region than in epicardium or endocardium and from differences in the time-course of final repolarization (phase 3) of the action potential of the three predominant ventricular cell types. The epicardial response is usually the first to repolarize and the M cell action potential the last. Full repolarization of epicardium coincides with the peak of the T wave and repolarization of the M cells coincides with the end of the T wave. The APD of the M cell therefore determines the duration of the QT interval under a wide variety of conditions, including changes in pacing rate, prematurity, alterations in $[K^+]_o$ and exposure to APD-prolonging drugs. Under these conditions, the T_{peak}–T_{end} interval provides an index of transmural dispersion of repolarization, which could prove valuable as a prognostic tool[33,53] as reported by Lubinski *et al.*[54].

Inscription of the U wave

The cellular basis for the U wave has been a matter of debate for over a century and remains so today. A significant part of the problem lies in the definition of the U wave. Recent work involving the arterially perfused wedge preparation indicates that what many clinicians refer to as an accentuated or inverted U wave is not a U wave, but rather a component of the T wave whose descending or ascending limb (especially during hypokalaemia) is interrupted (Fig. 6)[26,33]. A transient reversal in current flow across the wall due to shifting voltage gradients between epicardium and the M region

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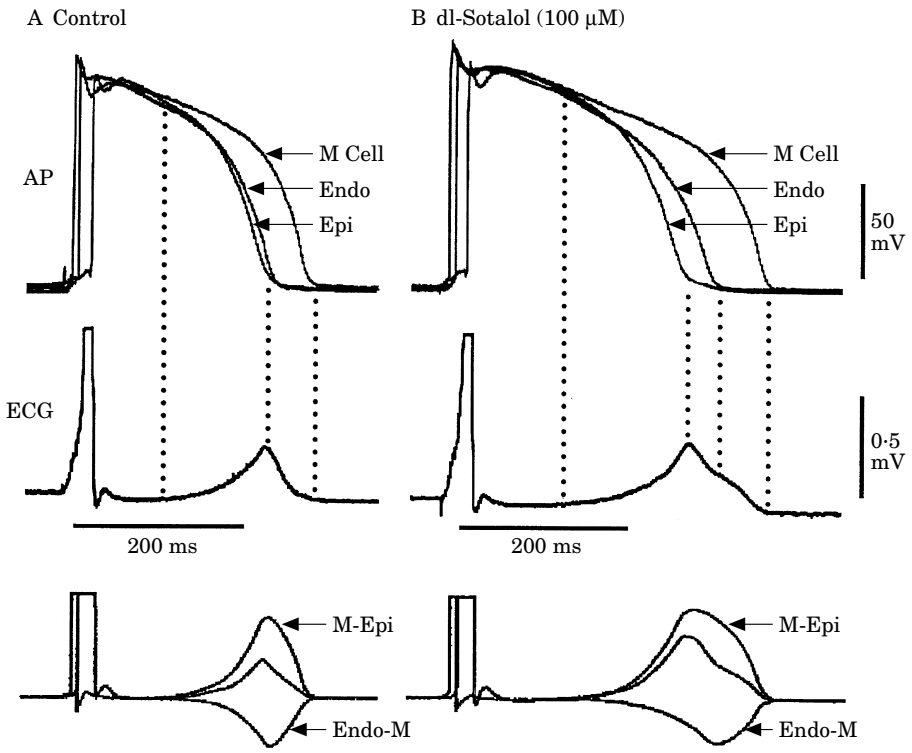

Figure 5 **Voltage gradients on either side of the M region are responsible for inscription of the electrocardiographic T wave. Top: Action potentials simultaneously recorded from endocardial, epicardial and M region sites of an arterially perfused canine LV wedge preparation. Middle: ECG recorded across the wedge. Bottom: Computed voltage differences between the epicardium and M region action potentials ($\Delta V_{M\text{-}Epi}$) and between the M region and endocardium responses ($\Delta V_{Endo\text{-}M}$). If these traces are representative of the opposing voltage gradients on either side of the M region, responsible for inscription of the T wave, then the weighted sum of the two traces should yield a trace (middle trace in bottom grouping) resembling the ECG, which it does. The voltage gradients are weighted to account for differences in tissue resistivity between M and Epi and Endo and M regions, thus yielding the opposing currents flowing on either side of the M region. A: Under control conditions the T wave begins when the plateau of epicardial action potential separates from that of the M cell. As epicardium repolarizes, the voltage gradient between epicardium and the M region continues to grow giving rise to the ascending limb of the T wave. The voltage gradient between the M region and epicardium ($\Delta V_{M\text{-}Epi}$) reaches a peak when the epicardium is fully repolarized — this marks the peak of the T wave. On the other end of the ventricular wall, the endocardial plateau deviates from that of the M cell, generating an opposing voltage gradient ($\Delta V_{Endo\text{-}M}$) and corresponding current that limits the amplitude of the T wave and contributes to the initial part of the descending limb of the T wave. The voltage gradient between the endocardium and the M region reaches a peak when the endocardium is fully repolarized. The gradient continues to decline as the M cells repolarize. All gradients are extinguished when the longest M cells are fully repolarized. B: D-sotalol (100 μM) prolongs the action potential of the M cell more than those of the epicardial and endocardial cells, thus widening the T wave and prolonging the QT interval. The greater separation of epicardial and endocardial repolarization times also gives rise to a notch in the descending limb of the T wave. Once again, the T wave begins when the plateau of epicardial action potential diverges from that of the M cell. The same relationships as described for panel A are observed during the remainder of the T wave. The d-sotalol-induced increase in dispersion of repolarization across the wall is accompanied by a corresponding increase in the T_{peak}-T_{end} interval in the pseudo-ECG. (Modified with permission[33].)**

and endocardium and the M region appear to underlie these phenomena. The data suggest that the 'pathophysiologic U wave' that develops under conditions of acquired or congenital LQTS is part of the T wave and that the various hump morphologies represent different levels of interruption of the ascending limb of the

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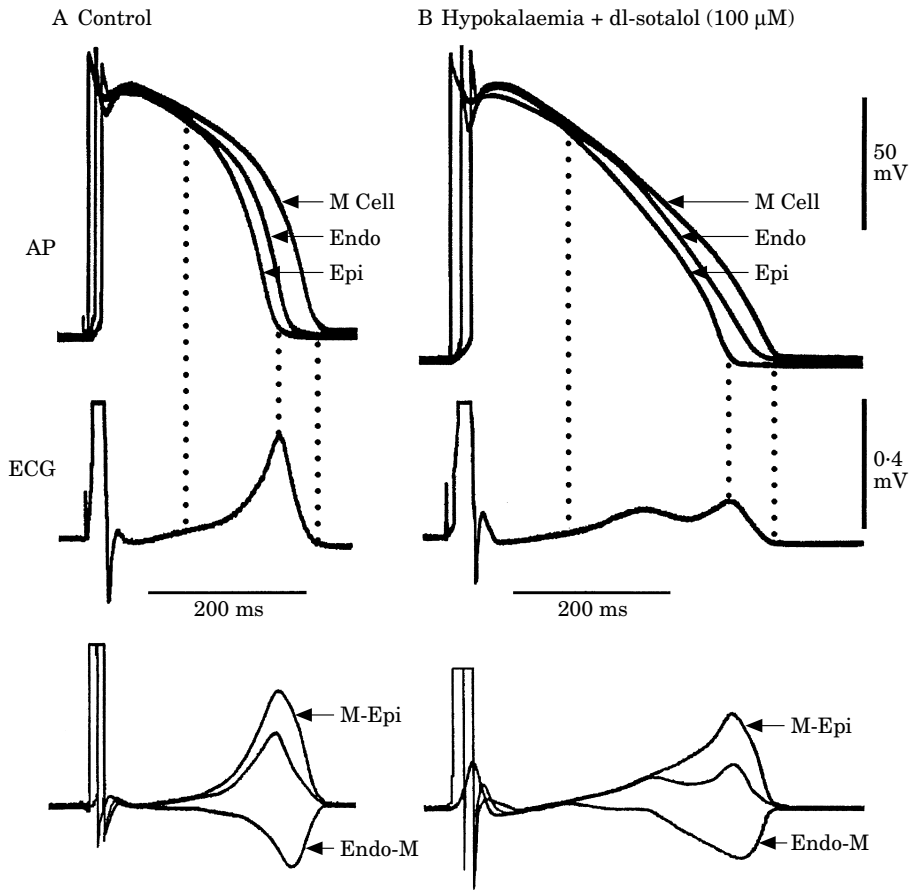

Figure 6 **Transient shift of voltage gradients on either side of the M region results in T wave bifurcation. The format is the same as in Fig. 5. All traces were simultaneously recorded form an arterially perfused LV wedge preparation. A: Control. B: In the presence of hypokalaemia ($[K^+]_o = 1{\cdot}5$ mM), the I_{Kr} blocker dl-sotalol (100 μM) prolongs the QT interval and produces a bifurcation of the T wave, a morphology some authors refer to as T-U complex. The rate of repolarization of phase 3 of the action potential is slowed giving rise to smaller opposing transmural currents that crossover producing a low amplitude bifid T wave. Initially the voltage gradient between the epicardium and M regions (M-Epi) is greater than that between endocardium and M region (Endo-M). When endocardium pulls away from the M cell, the opposing gradient (Endo-M) increases, interrupting the ascending limb of the T wave. Predominance of the M-Epi gradient is restored as the epicardial response continues to repolarize and the Epi-M gradients increases, thus resuming the ascending limb of the T wave. Full repolarization of epicardium marks the peak of the T wave. Repolarization of both endocardium and the M region contribute importantly to the descending limb. BCL = 1000 ms. (Modified with permission[33].)**

T wave, arguing for use of the term T2 in place of U to describe these events[33,55].

What then is responsible for the normal U wave, the very small distinct deflection following the T wave? The repolarization of the His–Purkinje system as previously suggested by Watanabe[56] remains a very plausible hypothesis. Repolarization of the Purkinje system is temporally aligned with the expected appearance of the U wave in the perfused wedge preparation[33]. A test of this hypothesis awaits the availability of an experimental model displaying a prominent U wave, although indirect support for the hypothesis has been presented[57,58].

The ability to distinguish a U wave from a second component of the T wave is of utmost importance when assessing the action of a drug on the QT interval. Mistaking a T wave component for a U wave can lead to a gross underestimation of the effect of a drug to prolong QTc and thus and potentially tragic underestimation of the drug's proarrhythmic potential.

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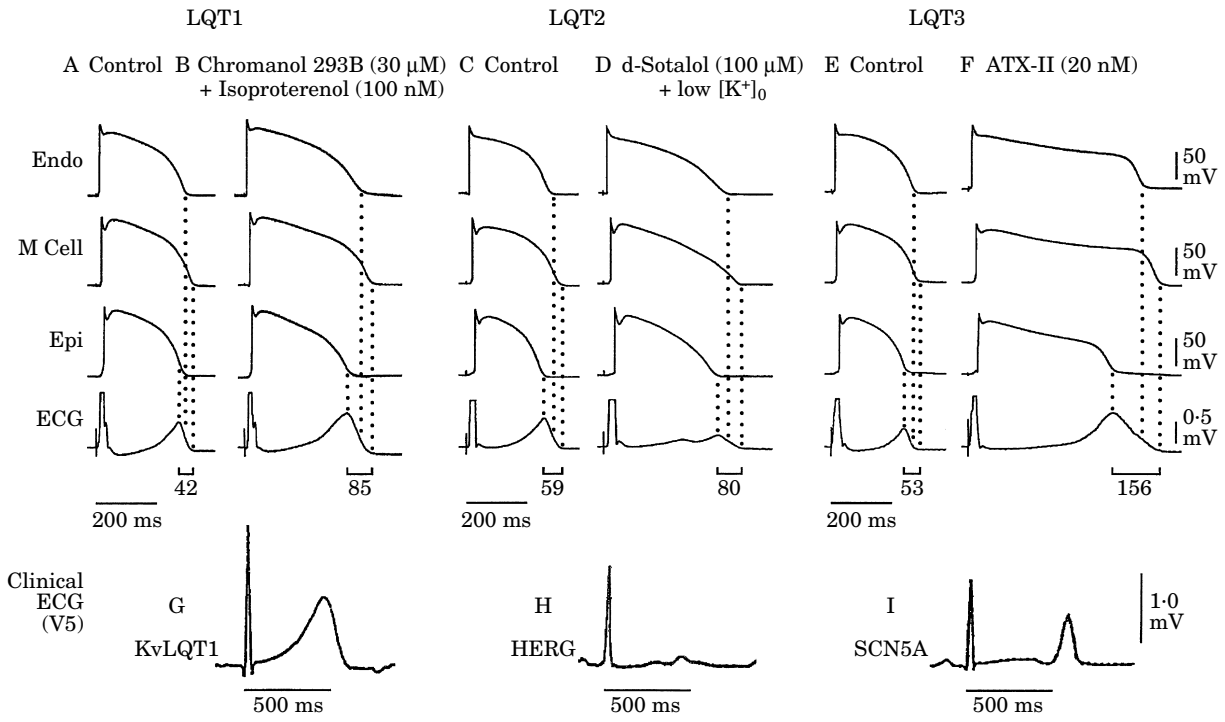

Figure 7 **Transmembrane action potentials and transmural electrocardiograms (ECG) in control and LQT1 (A and B), LQT2 (C and D), and LQT3 (E and F) models of LQTS (arterially perfused canine LV wedge preparations), and clinical ECG (lead V5) of patients with LQT1 (KvLQT1 defect) (G), LQT2 (HERG defect) (H) and LQT3 (SCN5A defect) (I) syndromes. Isoproterenol+chromanol 293B — an I_{Ks} blocker, d-sotalol+low $[K^+]_o$, and ATX-II — an agent that slows inactivation of late I_{Na} are used to mimic the LQT1, LQT2 and LQT3 syndromes, respectively. Panels A–F depict action potentials simultaneously recorded from endocardial (Endo), M and epicardial (Epi) sites together with a transmural ECG. BCL=2000 ms. In all cases, the peak of the T wave in the ECG is coincident with the repolarization of the epicardial action potential, whereas the end of the T wave is coincident with the repolarization of the M cell action potential. Repolarization of the endocardial cell is intermediate between that of the M cell and epicardial cell. Transmural dispersion of repolarization across the ventricular wall, defined as the difference in the repolarization time between M and epicardial cells, is denoted below the ECG traces. B: Isoproterenol (100 nM) in the presence of chromanol 293B (30 μM) produced a preferential prolongation of the APD of the M, resulting in an accentuated transmural dispersion of repolarization and broad-based T waves as commonly seen in LQT1 patients (G). D: d-Sotalol (100 μM) in the presence of low potassium (2 mM) gives rise to low-amplitude T waves with a notched or bifurcated appearance due to a very significant slowing of repolarization as commonly seen in LQT2 patients (H). F: ATX-II (20 nM) markedly prolongs the QT interval, widens the T wave, and causes a sharp rise in the dispersion of repolarization. ATX-II also produced a marked delay in onset of the T wave due to relatively large effects of the drug on the APD of epicardium and endocardium, consistent with the late-appearing T wave pattern observed in LQT3 patients (1). (Modified with permission[26,31].)**

Role of transmural heterogeneity of repolarization in the long QT syndrome

The congenital and acquired (drug-induced) long QT syndromes (LQTS) are characterized by the appearance of long QT intervals in the ECG and atypical polymorphic ventricular tachycardias displaying features of TdP[59–61]. As discussed above, electrical heterogeneity secondary to the presence of M cells within the ventricular wall contributes to the manifestation of normal and abnormal T waves in the ECG[14,18,26,33,62–64]. Preferential prolongation of the APD of cells in the M region appears to underlie LQTS, contributing to the development of long QT intervals, abnormal T waves and TdP. Support for these hypotheses has been advanced in studies involving the arterially perfused wedge preparation[14,26,31,33,65] which is capable of developing and sustaining a variety of arrhythmias, including TdP.

Congenital LQTS is caused by mutations in ion channel genes located on chromosomes 3, 7, II and 21, responsible for defects in the sodium channel (SCN5A, LQT3), the rapidly activating delayed rectifier channel (I_{Kr}) [HERG (human ether-à-gogo-related gene), LQT2 or KCNE2, LQT6] and the slowly activating delayed rectifier channel (I_{Ks}) (KvLQTl, LQTl or KCNE1, LQT5), respectively[66].

Experimental models have been developed to assess the contribution of electrical heterogeneity across the ventricular wall to the manifestation of the T wave and

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Table 4 Characteristics of LQT1, LQT2 and LQT3 models of LQTS in canine arterially-perfused left ventricular wedge preparations

	LQT1	LQT2	LQT3
ECG T wave pattern	Broad-based T wave	Low amplitude T wave, notched or birfurcated appearance	Late-appearing T wave
Rate dependence of QT interval	++	++	+++++
Sensitivity to catecholamines	+++++ (Sustained ↑ in TDR)	+++ (Transient ↑ in TDR)	– (↓ in TDR)
Torsades de Pointes (in the clinic)	Exercise-related	Startle alarm clock[77]	Rest/sleep
Effectiveness of beta-blockers	+++++	+++	–
Effectiveness of Na^+ channel blockers	+++	++++	+++++

TDR = transmural dispersion of repolarization.
+Small/low; +++++large/high.

to arrhythmogenesis under conditions of 'acquired' LQTS mimicking the genetic defects linked to the congenital syndrome (Fig. 7). I_{Ks} block with Chromanol 293B was used to mimic LQTl and the beta-adrenergic agonist, isoproterenol, was used to assess beta-adrenergic influence. I_{Ks} block alone produces a homogeneous prolongation of repolarization across the ventricular wall. This effect of the drug produces a significant prolongation of the QT interval, but no change in transmural dispersion. TdP does not occur spontaneously, nor can it be induced in the presence of I_{Ks} block alone. The addition of isoproterenol leads to abbreviation of epicardial and endocardial APD with little or no change or prolongation of the APD of the M cell, resulting in a marked augmentation of transmural dispersion of repolarization (TDR) and the development of spontaneous and stimulation-induced TdP[31]. These cellular changes generally give rise to a broad-based T wave and along QT interval characteristic of LQT1. The development of TdP in this model is exquisitely sensitive to beta-adrenergic stimulation consistent with the high sensitivity of congenital LQTS, LQTl in particular, to sympathetic stimulations[59–61,67,68]. These findings not only add to our understanding of the mechanism by which the sympathetic nervous system contributes to arrhythmogenesis in LQT1, but also highlight that QT prolongation per se is not arrhythmogenic unless it is accompanied by an increase in transmural (or other) dispersion of repolarization.

D-Sotalol, an I_{Kr} blocker, was used to mimic LQT2 and the most common form of acquired LQTS. In this experimental model, a greater prolongation of the M cell action potential and slowing of phase 3 of the action potential of all three cell types results in a low-amplitude T wave, long QT interval, large transmural dispersion of repolarization and the development of spontaneous as well as 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[26,33]. Beta-adrenergic agents such as isoproterenol further exaggerate transmural dispersion of repolarization, thus increasing the incidence of TdP[69].

ATX-II, a sea anemone toxin capable of increasing late I_{Na}, was used to mimic the LQT3 syndrome[26,70]. This toxin markedly prolongs the QT interval, delays the onset of the T wave, in some cases also widening it, and causes a sharp rise in transmural dispersion of repolarization as a result of a greater prolongation of the APD of the M cell. The greater effect of ATX-II to prolong the M cell is likely due to the presence of a larger late sodium current in the M cell[11]. 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 observation is consistent with the late-appearing T wave pattern and long isoelectric ST segment observed in patients with the LQT3 syndrome. Also concordant with the clinical presentation of LQT3, the wedge model displays a steep rate-dependence of the QT interval and develops TdP at slow rates. In this model, beta-adrenergic stimulation reduces transmural dispersion of repolarization by abbreviating the APD of the M cell more than that of epicardium or endocardium. Transmural dispersion of repolarization is thus reduced, as is the incidence of TdP.

While the beta-adrenergic blocker propranolol is protective in LQTl and LQT2 wedge models, it exerts an opposite effect in LQT3, acting to amplify transmural dispersion and to promote TdP[69]. Table 4 summarizes the distinctions in the characteristics and pharmacology of the three LQTS models. The electrocardiographic T wave patterns described are similar to those observed in patients with the respective genotype of the disease. Exceptions to these distinctive genotype-specific T wave morphologies are encountered in the wedge, as they are in the clinic.

The arrhythmia most commonly encountered in congenital and acquired LQTS is TdP, an atypical polymorphic ventricular tachycardia. TdP generally develops in patients receiving an I_{Kr} blocker, especially in the presence of hypokalaemia and slow heart rates or long pauses. These conditions are similar to those under which agents such as quinidine and d-sotalol induce EADs and triggered activity in isolated Purkinje fibres and M cells, suggesting a role for EAD-induced triggered activity in the genesis of TdP. An EAD-induced extrasystole is believed to be responsible for the

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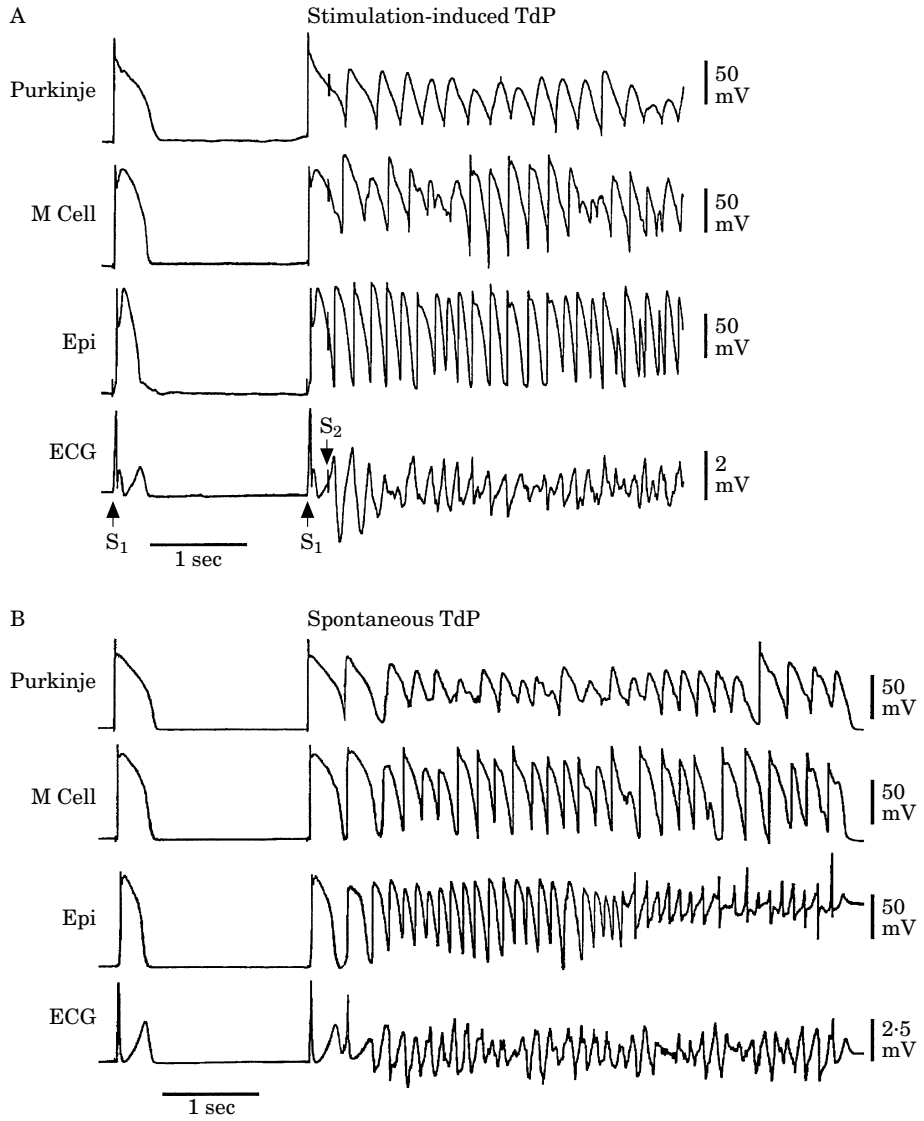

Figure 8 **Spontaneous and stimulation-induced polymorphic ventricular tachycardia with features of torsade de pointes (TdP). A: Stimulation-induced TdP in a LV wedge preparation pretreated with dl-sotalol (100 µmol . l^{-1}). S1 − S1 = 2000 ms; S1 − S2 = 250 ms. S2 was applied to epicardium. B: Spontaneous TdP in a preparation pre-treated with dl-sotalol (100 µmol . l^{-1}). BCL = 2000 ms. A spontaneous premature beat with a coupling interval of 348 ms, probably originating from subendocardial Purkinje system, initiates an episode of torsade de pointes.**

premature beat that initiates TdP, but the maintenance of the arrythmia appears to be due to a circus re-entry mechanism[8,18,22,26,27,31,33,41,65,71–76]. TdP develops spontaneously in all three wedge models and can be readily induced by introduction of a single premature beat when TDP does not occur spontaneously (Fig. 8). The triggering extrastimulus is most effective when applied to the site of earliest repolarization, usually on the epicardial surface.

The available data support the hypothesis outlined in Fig. 9. The hypothesis presumes the presence of electrical heterogeneity under baseline conditions, principally in the form of transmural dispersion of repolarization. This intrinsic heterogeneity can be amplified by agents that reduce net repolarizing current via a reduction in I_{Kr} or I_{Ks} or augmentation of late I_{Ca} or late I_{Na} or by ion channel mutations that affect these currents and are responsible for the various forms of LQTS. I_{Kr} blockers and LQT2 mutations or late I_{Na} promoters and LQT3 mutations produce a preferential prolongation of the M cell action potential. As a consequence, the QT interval prolongs and is accompanied by a dramatic increase in transmural dispersion of repolarization, which creates a vulnerable window for the development of re-entry. The reduction in net repolarizing current also leads to the development of EAD-induced triggered activity in M

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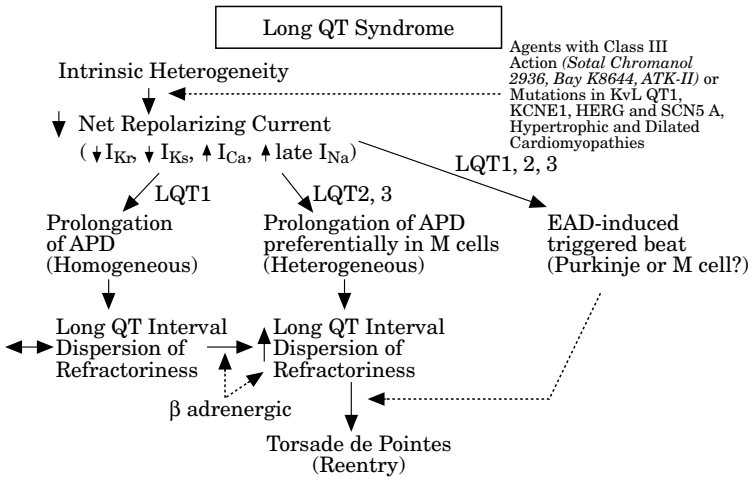

Figure 9 **Proposed cellular mechanism for the development of torsade de pointes in the LQT1, 2 and 3 forms of the long QT syndrome.**

and Purkinje cells, which provide the extrasystole that triggers TdP when it falls within the vulnerable period. Beta-adrenergic agonists further amplify transmural heterogeneity (transiently) in the case of I_{Kr} block and LQT2, but reduce it in the case of I_{Na} promoters and LQT3[69]. In contrast, I_{Ks} blockers or LQTl mutations; cause a homogeneous prolongation of APD throughout the ventricular wall, leading to a prolongation of the QT interval but with no increase in transmural dispersion of repolarization. TdP does not occur spontaneously nor can it be induced by programmed stimulation under these conditions until beta-adrenergic agonist is introduced. The beta-adrenergic agonist dramatically increases transmural dispersion of repolarization and refractoriness under these conditions by abbreviating the APD of epicardium and endocardium, thus creating a vulnerable window that an EAD-induced triggered response can capture to generate TdP.

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