The Role of Spatial Dispersion of Repolarization in Sudden Cardiac Death

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ABSTRACT

Spatial dispersion of repolarization in the form of transmural, trans-septal and apico-basal dispersion of repolarization creates voltage gradients that inscribe the J wave and T wave of the ECG. Amplification of this spatial dispersion of repolarization underlies the development of life-threatening ventricular arrhythmias associated with inherited ion channelopathies including the long QT, short QT and Brugada syndromes as well as catecholaminergic polymorphic ventricular tachycardia (CPVT). In the long QT Syndrome, amplification of TDR is often secondary to preferential prolongation of the action potential duration (APD) of M cells, whereas in the Brugada Syndrome, it is thought to be due to selective abbreviation of the APD of right ventricular (RV) epicardium. Preferential abbreviation of APD of either endocardium or epicardium appears to be responsible for amplification of TDR in the short QT syndrome. In catecholaminergic polymorphic VT, the reversal of the direction of activation of the ventricular wall is responsible for the increase in TDR. In conclusion, the long QT, short QT, Brugada and catecholaminergic VT syndromes are pathologies with very different phenotypes and etiologies, but which share a common final pathway in causing sudden death.

Heterogeneities of ventricular repolarization have long been implicated in arrhythmogenesis. This review focuses on the role of spatial dispersion of repolarization in the form of transmural dispersion of repolarization (TDR) to inscribe the J wave and T wave of the ECG and on the role of amplification of these heterogeneities on the development of life-threatening ventricular arrhythmias associated with inherited ion channelopathies (**Table 1**) such as the long QT, short QT and Brugada syndromes as well as catecholaminergic polymorphic ventricular tachycardia (CPVT).

Table 1. Genetic Disorders Caused by Ion Channelopathies

	Rhythm		Inheritance	Locus	Ion Channel	Gene
Long QT syndrome	(RW)	TdP	AD			
	LQT1			11p15	I_{Ks}	*KCNQ1, KvLQT1*
	LQT2			7q35	I_{Kr}	*KCNH2, HERG*
	LQT3			3p21	I_{Na}	*SCN5A, $Na_v1.5$*
	LQT4			4q25		*ANKB, ANK2*
	LQT5			21q22	I_{Ks}	*KCNE1, minK*
	LQT6			21q22	I_{Kr}	*KCNE2, MiRP1*
	LQT7	(Andersen-Tawil Syndrome)		17q23	I_{K1}	*KCNJ2, Kir 2.1*
	LQT8	(Timothy Syndrome)		6q8A	$I_{Ca\text{-}L}$	*CACNA1C, $Ca_v1.2$*
	LQT9			3p25	I_{Na}	*CAV3, Caveolin-3*
	LQT10			11q23.3	I_{Na}	*SCN4B. Na_vb4*
LQT syndrome (JLN)		TdP	AR	11p15	I_{Ks}	*KCNQ1, KvLQT1*
				21q22	I_{Ks}	*KCNE1, minK*
Brugada syndrome	BrS1	PVT	AD	3p21	I_{Na}	*SCN5A, $Na_v1.5$*
	BrS2	PVT	AD	3p24	I_{Na}	GPD1L
Short QT syndrome	SQT1	VT/VF	AD	7q35	I_{Kr}	*KCNH2, HERG*
	SQT2			11p15	I_{Ks}	*KCNQ1, KvLQT1*
	SQT3		AD	17q23.1-24.2	I_{K1}	*KCNJ2, Kir2.1*
Catecholaminergic VT	CPVT1	VT	AD	1q42-43		*RyR2*
	CPVT2	VT	AR	1p13-21		*CASQ2*

Abbreviations: AD: autosomal dominant, AR: autosomal recessive, JLN: Jervell and Lange–Nielsen, LQT: Long QT, RW: Romano-Ward, TdP: Torsade de Pointes, VF: ventricular fibrillation, VT: ventricular tachycardia, PVT: Polymorphic VT

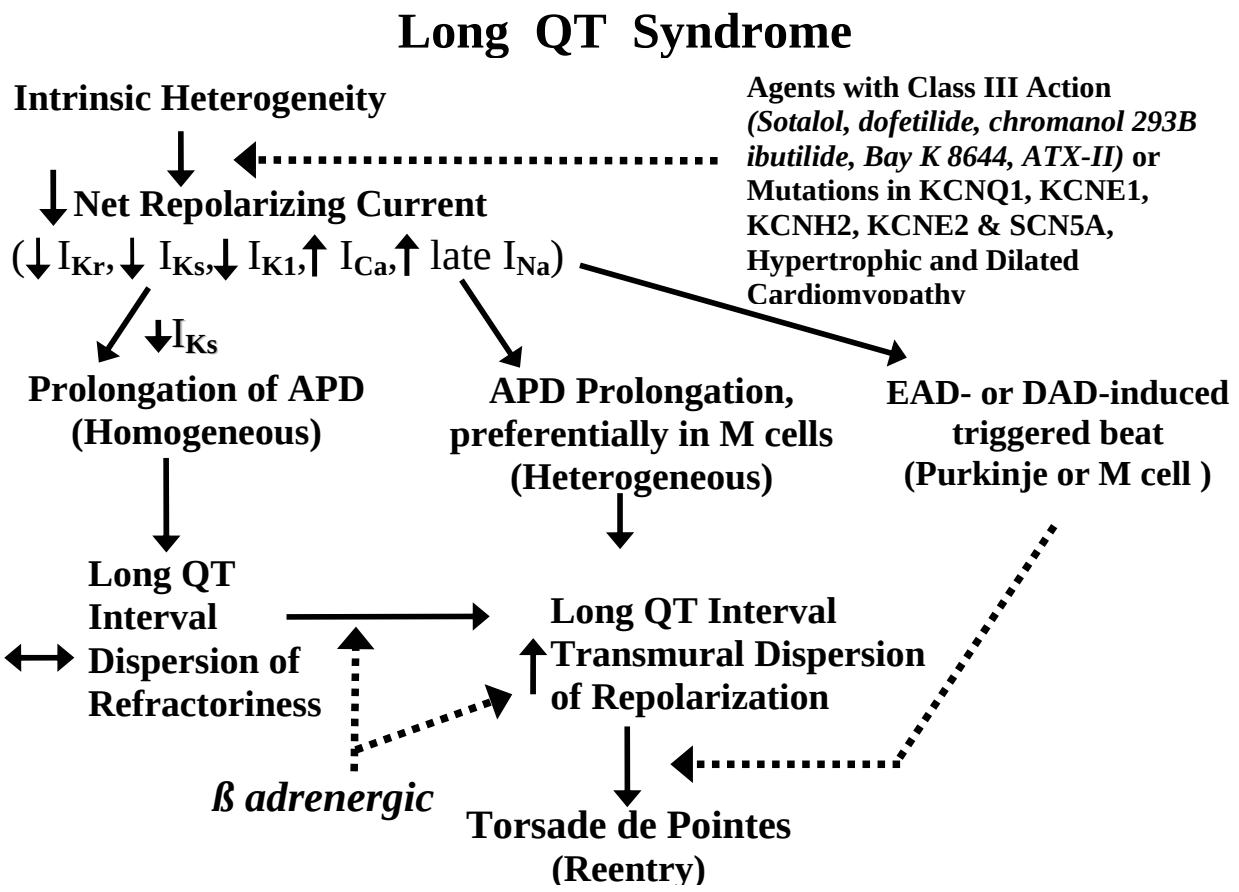

Figure 1. Proposed cellular mechanism for the development of Torsade de Pointes in the long QT syndromes.

Electrical Heterogeneities Intrinsic to Ventricular Myocardium

It is now well established that that ventricular myocardium is comprised of at least three electrophysiologically and functionally distinct cell types: epicardial, M and endocardial cells.[1, 2] 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 (4-AP) sensitive transient outward current (I_{to}), giving the action potential a spike and dome or notched configuration. These regional differences in I_{to}, first suggested on the basis of action potential data [3], have now been directly demonstrated in canine [4], feline [5], rabbit [6], rat [7], and human [8, 9] ventricular myocytes.

Differences in the magnitude of the action potential notch and corresponding differences in I_{to} have also been described between right and left ventricular epicardial and M cells.[10, 11]. 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.

Between surface epicardial and endocardial layers are layers of 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, 12, 13]. 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_{Ks}) [14], a larger late sodium current (late I_{Na}) [15] and a larger Na-Ca exchange current (I_{Na-Ca})[16]. In the canine heart, the rapidly activating delayed rectifier (I_{Kr}) and inward rectifier (I_{K1}) currents are similar in the three transmural cell types (**Fig. 1**). Transmural and apico-basal differences in the density of I_{Kr} channels have been described in the ferret heart [17]. I_{Kr} message and channel protein are much larger in the ferret epicardium. I_{Ks} is larger in M cells isolated from the right vs. left ventricles of the dog [11]. I_{Ca} has been shown to be similar among cells isolated from epicardium, M, and endocardial regions of the left ventricular wall.[18, 19] 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 comprised of two components: a Ni^{2+}-sensitive T-type current and a tetrodotoxin-sensitive Ca2+ current. [20]

Although, histologically M cells are similar to epicardial and endocardial cells, electrophysiologically and pharmacologically, they appear to be a hybrid between Purkinje and ventricular cells.[21] Like Purkinje fibers, M cells show a prominent APD prolongation and develop early afterdepolarizations (EAD) in response to I_{Kr} blockers, whereas epicardium and endocardium do not. Like Purkinje fibers, M cells develop delayed afterdepolarizations (DAD) in response to agents that calcium load or overload the cardiac cell; epicardium and endocardium do not. Unlike Purkinje fibers, M cells display an APD prolongation in response to I_{Ks} blockers; epicardium and endocardium also show an increase in APD in response to I_{Ks} blockers. Purkinje and M cells also respond differently to α adrenergic agonists. α_1 Adrenoceptor stimulation produces APD prolongation in Purkinje fibers, but abbreviation in M cells, and little or no change in endocardium and epicardium [22].

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 BCLs $\geq$ 2000 msec) are

often localized in the deep subendocardium to midmyocardium in the anterior wall, [23] deep subepicardium to midmyocardium in the lateral wall [12] and throughout the wall in the region of the right ventricular (RV) outflow tracts.[2] M cells are also present in the deep cell layers of endocardial structures, including papillary muscles, trabeculae and the interventricular septum [24]. Unlike Purkinje fibers, M cells are not found in discrete bundles or islets [24, 25], 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 [4, 12-14, 23-43].

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.[41, 44] Studies involving the arterially-perfused wedge have shown that currents flowing down voltage gradients on either side of the M region are in large part responsible for the T wave.[41] The interplay between these opposing forces establishes the height and width of the T wave and the degree to which either the ascending or descending limb of the T wave is interrupted, leading to a bifurcated or notched appearance of the T wave.[41] The voltage gradients result from a more positive plateau potential in the M region than in epicardium or 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 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 determine the QT interval. The interval between the peak and end of the T wave (Tp-Te) has been suggested to provide an **index** of transmural dispersion of repolarization, which may be of prognostic value. [41, 45]

Although apico-basal repolarization gradients have been suggested to play a prominent role in the registration of the T wave,.[44, 46] studies involving coronary-perfused wedge preparations suggest little or no contribution.[41]

The long QT syndrome

Prolongation of the action potential duration of the M cell usually underlies the prolongation of the QT interval on the surface ECG, the time interval between ventricular depolarization and repolarization. Prolongation of the QT can occur as a consequence of congenital defects or in response to drugs that prolong the APD via a reduction in I_{Ks}, I_{Kr} or the inward rectifier potassium

current (I_{K1}), or an increase in calcium current (I_{Ca}) or late sodium current (I_{Na}). The inherited forms of the long QT syndrome (LQTS) are phenotypically and genotypically diverse, but have in common the appearance of long QT interval in the ECG, an atypical polymorphic ventricular tachycardia known as Torsade de Pointes, and, in many but not all cases, a relatively high risk for sudden cardiac death.[47-49] Congenital LQTS is subdivided into ten genotypes distinguished by mutations in at least seven different ion genes and an structural anchoring protein located on chromosomes 3, 4, 6, 7, 11, 17 and 21 (**Table 1**).[50-57] Timothy syndrome, also referred to as LQT8, is a rare congenital disorder characterized by multi-organ dysfunction including prolongation of the QT interval, lethal arrhythmias, webbing of fingers and toes, congenital heart disease, immune deficiency, intermittent hypoglycemia, cognitive abnormalities, and autism. Timothy syndrome has been linked to loss of voltage-dependent inactivation due to mutations in $Ca_v1.2$, the gene that encodes for an α subunit of the calcium channel.[58] The most recent genes associated with LQTS are *CAV3* which encodes caveolin-3 and *SCN4B* which encodes Na_vB4, an auxiliary subunit of the cardiac sodium channel. Mutations in both genes produce a gain of function in late I_{Na} , causing an LQT3-like phenotype.[56, 57]

Two patterns of inheritance have been identified: 1) a rare autosomal recessive disease associated with deafness (Jervell and Lange-Nielsen), caused by 2 genes that encode for the slowly activating delayed rectifier potassium channel (KCNQ1 and KCNE1); and 2) a much more common autosomal dominant form known a the Romano Ward syndrome, caused by mutations in 10 different genes, including *KCNQ1* (KvLQT1; LQT1); *KCNH2* (HERG;LQT2); *SCN5A* ($Na_v1.5$; LQT3); *ANKB* (LQT4); *KCNE1* (minK; LQT5); *KCNE2* (MiRP1; LQT6); *KCNJ2* (LQT7; Andersen's syndrome), *CACNA1C* ($Ca_v1.2$; LQT8; Timothy Syndrome), *CAV3* (Caveolin-3; LQT9) and *SCN4B* (Na*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[59]. 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, ICD and/or cardiac sympathetic denervation may be therapeutic alternatives [60, 61].

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[62] 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.[63-67] Most of the drugs that cause acquired LQTS, block I_{Kr}, many also block I_{Ks}, and some augment late I_{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 in some cases may have a genetic predisposition.

The ability of genetic mutations and drugs to amplify 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, trans-septal or apico-basal dispersion of repolarization, and the development of early afterdepolarization (EAD)-induced triggered activity underlie the substrate and trigger for the development of Torsade de Pointes arrhythmias observed under LQTS conditions.[68, 69] Models of the LQT1, LQT2, LQT3, and LQT7 forms of the long QT syndrome have been developed using the canine arterially perfused left ventricular wedge preparation.[70-72] 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 transmural dispersion of repolarization (TDR), which contributes to the development of spontaneous as well as stimulation-induced Torsade de Pointes (TdP).[34, 39, 73]

The distinctive characteristics of the M cells are at the heart of the long QT syndrome. 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. [2, 12, 74] 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_{Ks} and a larger late I_{Na} and $I_{Na\text{-}Ca}$[14-16] compared to epicardial and endocardial cells. These ionic distinctions sensitize the M cells to a variety of pharmacological agents and pathophysiological states. Agents that block I_{Kr}, I_{Ks} or increase I_{Ca} or late I_{Na} generally produce a much greater prolongation of the APD of the M cell than of epicardial or endocardial cells.

Experimental models that mimic the clinical congenital syndromes with respect to prolongation of the QT interval, T wave morphology, rate dependence of QT have also been helpful in elucidation of the basis for sympathetic nervous system influences.[23, 34, 39-41]

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 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 transmural dispersion of repolarization (TDR) and the development of spontaneous and stimulation-induced TdP [39]. 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 β

adrenergic stimulation, consistent with a high sensitivity of congenital LQTS, LQT1 in particular, to sympathetic stimulation [47-49, 75, 76].

I_{Kr} block using d-Sotalol has been used to mimic LQT2 and provides a model of the most common form of acquired (drug-induced) LQTS. 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 hypokalemia 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 [34, 41]. Isoproterenol further exaggerates transmural dispersion of repolarization, thus increasing the incidence of TdP.[73]

ATX-II, an agent that increases late I_{Na}, is used to mimic LQT3 [34]. 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 transmural dispersion of repolarization 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 sodium current in the M cell [15]. 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, β adrenergic influence in the form of isoproterenol **reduces** transmural dispersion of repolarization by abbreviating the APD of the M cell more than that of epicardium or endocardium, and thus reducing the incidence of TdP. While the β 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.[73]

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 (**Fig. 3**) and in the clinic. [69, 77] In LQT1, β adrenergic stimulation induces an increase in TDR that is most prominent during the first two minutes, 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 less than 2 minutes. 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[69, 76, 78].

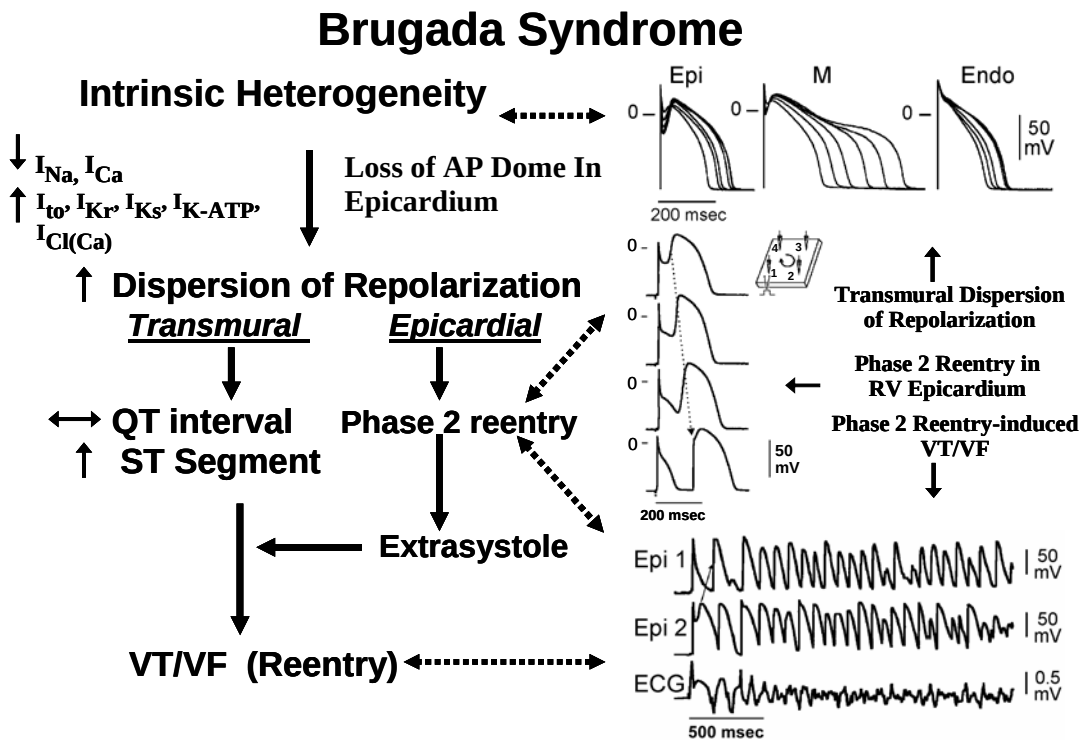

Figure 3. Proposed Mechanism for the Brugada syndrome. A shift in the balance of currents serves to amplify existing heterogeneities by causing loss of the action potential dome at some epicardial, but not endocardial sites. A vulnerable window develops as a result of the dispersion of repolarization and refractoriness within epicardium as well as across the wall. Epicardial dispersion leads to the development of phase 2 reentry, which provides the extrasystole that captures the vulnerable window and initiates VT/VF via a circus movement reentry mechanism. Modified from [170], with permission.

β blockers are considered the first line of therapy in LQT1 and LQT2, but have not been shown to be of benefit in LQT3. Preliminary data suggest LQT3 patients might benefit from Na^+ channel blockers, such as mexiletine and flecainide but long-term data are not yet available.[79, 80] Experimental data have shown that mexiletine reduces transmural dispersion and prevents TdP in LQT3 as well as LQT1 and LQT2, suggesting that agents that block the late sodium current may be effective in all forms of LQTS.[34, 39] These observations suggest that a combination of β blockers and late sodium channel blockers may confers more protection in LQT1 and LQT2 than β blockade alone. The anti-anginal ranolazine, a potent blocker of late I_{Na}, has been shown to be very

effective in suppressing TdP in experimental models of LQT1, 2 and 3. [81-84] Clinical data are not available as yet.

Tpeak–Tend interval has been shown to provide a measure of transmural dispersion of repolarization in the wedge preparation.[2] In the intact heart, such equivalency is not to be expected,[85] yet we hypothesize that Tpeak-Tend may provide an important non-invasive index of changes in spatial dispersion of repolarization, particularly TDR. The available data suggest that Tpeak-Tend measurements might best be limited to precordial leads (V1-V6) since these leads more accurately reflect transmural dispersion of repolarization. Recent studies have provided guidelines for the estimation of transmural dispersion of repolarization in the case of more complex T waves, including negative, biphasic and triphasic T waves.[86] 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 transmural dispersion of repolarization.

The clinical applicability of these concepts remains to be carefully validated. Significant progress towards validation of the Tpeak-Tend interval as an index of transmural dispersion has been advanced in a number of studies. Lubinski et al.[87] demonstrated that this interval is increased in patients with congenital long QT syndrome. Recent studies suggest that the Tpeak-Tend interval may be a useful index of transmural dispersion and thus may be prognostic of arrhythmic risk under a variety of conditions.[88-93] Takenaka et al. recently demonstrated exercise-induced accentuation of the Tpeak-Tend interval in LQT1 patients, but not LQT2.[92] These observations coupled with those of Schwartz et al.[78] demonstrating an association between exercise and risk for TdP in LQT1, but not LQT2, patients, once again point to the potential value of Tpeak–Tend in forecasting risk for the development of TdP. Direct evidence in support of Tpeak-Tend as an index to predict TdP in patients with long QT syndrome was provided by Yamaguchi and co-workers.[94] These authors concluded that Tpeak-Tend is more valuable than QTc and QT dispersion as a predictor of Torsade de Pointes (TdP) in patients with acquired LQTS. Shimizu et al. demonstrated that Tpeak-Tend, but not QTc, predicted sudden cardiac death in patients with hypertrophic cardiomypathy.[91] Most recently, Watanabe et al. demonstrated that prolonged Tpeak-Tend is associated with inducibility as well as spontaneous development of VT in high risk patients with organic heart disease.[93] While 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 QT prolongation underlies the substrate responsible for the development of TdP.[68, 81, 95-97]

Fig. 1 presents a working hypothesis for our understanding of the mechanisms underlying LQTS-related TdP based on available data. The hypothesis presumes the presence of electrical

heterogeneity in the form of transmural or trans-septal dispersion of repolarization under baseline conditions and the amplification of TDR by agents that reduce net repolarizing current via a reduction in I_{Kr} or I_{Ks} or augmentation of I_{Ca} or late I_{Na}. Conditions that cause a reduction in I_{Kr} or augmentation of late I_{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 transmural dispersion of repolarization, thus creating a vulnerable window for the development of reentry. The reduction in net repolarizing current also predisposes to the development of EAD-induced triggered activity in M and Purkinje cells, which provide the extrasystole that triggers TdP when it falls within the vulnerable period. β adrenergic agonists further amplify transmural heterogeneity (transiently) in the case of I_{Kr} block, but reduce it in the case of I_{Na} agonists. [32, 73]

Although conditions that prolong QT are often 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.[98] 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.[99] In a dog model of chronic complete atrioventricular block and acquired LQTS, 6 weeks of amiodarone was shown to produce a major QT prolongation without producing TdP. In contrast, after 6 weeks of dronedarone, TdP occurred in 4 of 8 dogs displaying the highest spatial dispersion of repolarization (105±20 ms).[100] 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 msec. [38] 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_{Ks}, I_{Kr}, and late I_{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, another agent that blocks both inward and outward currents, produces a biphasic concentration-dependent prolongation of the QT interval. 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 prolong QT, but reduced TDR, thereby preventing TdP induction.[95] 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.

The I_{Ks} blocker, Chromanol 293B, is another agent that increases QT without augmenting TDR. Chromanol 293B prolongs APD of the 3 cell types homogeneously, neither increasing TDR nor widening the T wave. TdP is not observed under these conditions. Although an

arrhythmogenic substrate is not present with I_{Ks} 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.[73] TdP 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.

Thus, QT prolonging agents display very different concentration-dependent behavior. Pure I_{Kr} 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 approximately 90 msec, 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. TdP occurs when and if TDR reaches the threshold value. Still 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_{Ks} 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 the QT interval that is not associated with an increase in TDR. TdP rarely, if ever, occurs under these conditions.

Thus, TdP is not produced by drugs that cause a dose-dependent prolongation of QT but a reduction of TDR or little or no increase in TDR. Taken together these findings indicate that arrhythmogenesis in the long QT syndromes is not due to prolongation of QT interval but rather to the increase in TDR that often accompanies prolongation of the QT interval. The ability of sympathetic influences to dramatically increase TDR also explains why LQT1 and LQT2 patients are so sensitive to sympathetic stimulation.

Short QT Syndrome

QT intervals at both extremes of the normal range are now recognized to be associated with sudden cardiac death. The Short QT syndrome (SQTS), first proposed as a clinical entity by Gussak et al. in 2000,[101] is an inherited syndrome characterized by a QTc $\leq$ 320 msec and high incidence of VT/VF in infants, children and young adults.[102] The familial nature of this sudden death syndrome was highlighted by Gaita et al. in 2003.[103] The first genetic defect responsible for the short QT syndrome (SQTS1), reported by Brugada et al. in 2004, involved two different

missense mutations (substitution of one amino acid for another) resulting in the same amino acid substitution in HERG (N588K), which caused a gain of function in the rapidly activating delayed rectifier channel, $I_{Kr.}$[104] A second gene was recently reported by Bellocq et al. (SQTS2) [105] A missense mutation in KCNQ1 (KvLQT1) caused a gain of function in I_{Ks}. A third gene (SQT3), recently identified, involves KCNJ2, the gene that encodes for the inward rectifier channel. Mutations in KCNJ2 caused a gain of function in I_{K1}, leading to an abbreviation of QT interval. SQT3 is associated with QTc intervals <330 msec, not quite as short as SQT1, and SQT2.

The short QT syndrome is also characterized by the appearance of tall peaked symmetrical T waves in the ECG. The augmented Tpeak-Tend interval associated with this electrocardiographic feature of the syndrome suggests that TDR is significantly increased.

Studies employing the left ventricular wedge model of the short QT syndrome have provided evidence in support of the hypothesis that an increase in outward repolarizing current can preferentially abbreviate endocardial/M cell thus increase TDR and creating the substrate for reentry.[106] The potassium channel opener pinacidil used in this study caused a heterogeneous abbreviation of APD among the different cell types spanning the ventricular wall, thus creating the substrate for the genesis of VT under conditions associated with short QT intervals. Polymorphic VT could be readily induced with programmed electrical stimulation. The increase in TDR was further accentuated by isoproterenol, leading to easier induction and more persistent VT/VF. It is noteworthy that an increase of TDR to values greater than 55 msec was associated with inducibility of VT/VF. In LQTS models, a TDR of >90 msec is required to induce TdP. The easier inducibility in SQTS is due to the reduction in the wavelength (product of refractory period and conduction velocity) of the reentrant circuit, which reduces the pathlength required for maintenance of reentry.[106]

Brugada Syndrome

In that the Brugada syndrome is believed to be secondary to an exaggeration of the J wave, it seems appropriate to first discuss the basis for the J wave of the ECG. The presence of a prominent action potential notch in epicardium but not endocardium gives rise to a transmural voltage gradient during ventricular activation that manifests as a late delta wave following the QRS or what more commonly is referred to as a J wave [107] or Osborn wave. A distinct J wave is often observed under baseline conditions in the ECG of some animal species, including dogs and baboons. Humans more commonly display a J point elevation rather than a distinct J wave. A prominent J wave in the human ECG is considered pathognomonic of hypothermia [108-110, 110] or hypercalcemia. [111, 112]

A transmural gradient in the distribution of I_{to} is responsible for the transmural gradient in the magnitude of phase 1 and action potential notch, which in turn gives rise to a voltage gradient across the ventricular wall responsible for the inscription of the J wave or J point elevation in the ECG.[3, 4, 113] Direct evidence in support of the hypothesis that the J wave is caused by a transmural gradient in the magnitude of the I_{to}-mediated action potential notch derives from experiments conducted in the arterially-perfused right ventricular wedge preparation showing a correlation between the amplitude of the epicardial action potential notch and that of the J wave recorded during interventions that alter the appearance of the electrocardiographic J wave, including hypothermia, premature stimulation (restitution), and block of I_{to} by 4-aminopyridine (4-AP). [107]

The molecular basis for the transmural distribution of I_{to} has long been a subject of debate. The transmural gradient of I_{to} in dog has been ascribed to a transmural distribution of KCND3 gene (Kv4.3), which encodes the α subunit of the I_{to} channel[114] and a transmural gradient of KChIP2, a β subunit that coassembles with and serves as a chaperone for Kv4.3 [115]. The steep transmural gradient of I_{to} suggests that spatial patterning of I_{to} is highly regulated in mammalian cardiac myocytes. However, very little is known about transcriptional regulation of I_{to} and its components. Recently, a transcriptional factor, Iroquois 5, was described and shown to regulate KCND2 expression [116]. The Iroquois homeobox (Irx) genes encode a conserved family of transcription factors that specify the identity of diverse territories in the heart. One of the members of this family, the homeodomain transcription factor 5 (IRX5), has been shown to contribute to the cardiac repolarization gradient. IRX5 causes repression of Kv4.2 expression by recruiting mBop (a cardiac transcriptional repressor), thus forming an inverse I_{to} gradient that contributes to coordinated contraction of the ventricular wall [18]. In the canine heart, IRX5 is also expressed in an endocardial-to-epicardial gradient, suggesting that it may regulate expression of Kchip2 and/or KCND3 genes.

Myocytes isolated from the epicardial region of the left ventricular wall of the rabbit show a higher density of cAMP-activated chloride current when compared to endocardial myocytes. [117] I_{to2}, initially ascribed to a K^+ current, is now thought to be primarily due to the calcium-activated chloride current ($I_{Cl(Ca)}$) is also thought to contribute to the action potential notch, but it is not known whether this current, differs among the three ventricular myocardial cell types. [118]

Transmural activation within the thin wall of RV is relatively rapid causing the J wave to be buried inside the QRS. Thus, although the action potential notch is most prominent in right ventricular epicardium, right ventricular myocardium would be expected to contribute relatively little to the manifestation of the J wave under normal conditions. These observations are consistent with the manifestation of the J wave in ECG leads in which the mean vector axis is transmurally

oriented across the left ventricle and septum. Accordingly, the J wave in the dog is most prominent in leads II, III, aVR, aVF, and mid to left precordial leads V_3 through V_6. A similar picture is seen in the human ECG.[112, 119] In addition, vectorcardiography indicates that the J wave forms an extra loop that occurs at the junction of the QRS and T loops.[120] It is directed leftward and anteriorly, which explains its prominence in leads associated with the left ventricle.

To our knowledge, the first description of the J wave was in the 1920s in animal experiments involving hypercalcemia.[111] The first extensive description and characterization appeared 30 years later by Osborn in a study involving experimental hypothermia in dogs.[121] The appearance of a prominent J wave in the clinic is typically associated with pathophysiological conditions, including hypothermia[108, 119] and hypercalcemia [111, 112]. The prominent J wave induced by hypothermia is the result of a marked accentuation of the spike-and-dome morphology of the action potential of M and epicardial cells (i.e., an increase in both width and magnitude of the notch). In addition to inducing a more prominent notch, hypothermia produces a slowing of conduction which permits the epicardial notch to clear the QRS so as to manifest a distinct J wave. Hypercalcemia-induced accentuation of the J wave[111, 112, 122] may also be explained on the basis of an accentuation of the epicardial action potential notch, possibly as a result of an augmentation of the calcium-activated chloride current and a decrease in I_{Ca}.[123] Accentuation of the action potential notch also underlies the electrocardiographic and arrhythmogenic manifestations of the Brugada syndrome.

The Brugada syndrome is characterized by an accentuated ST segment elevation or J wave appearing principally in the right precordial leads (V1-V3), often followed by a negative T wave. The syndrome, first described in 1992, is generally associated with a high incidence of sudden cardiac death secondary to a rapid polymorphic VT or VF.[124] The average age at the time of initial diagnosis or sudden death is 40±22. The youngest patient diagnosed with the syndrome is 2 days of age, and the oldest is 84.

The prevalence of the Brugada syndrome is estimated at 1-5 per 10,000 inhabitants worldwide. The frequency is lower in western countries and higher ($\geq$5 per 10,000) in Southeast Asia, especially Thailand and the Philippines where Brugada syndrome is considered to be the major cause of sudden death in young individuals. In these countries, the syndrome is often referred to as Sudden Unexplained Nocturnal Death Syndrome (SUNDS).[125, 126]

Brugada syndrome is inherited via an autosomal dominant mode of transmission. The first gene to be linked to the Brugada syndrome is SCN5A, the gene encoding for the α subunit of the cardiac sodium channel gene [127]. Mutations in SCN5A are also responsible for the LQT3 form of the long QT syndrome and cardiac conduction disease. A number of mutations have been reported to cause overlapping syndromes; in some cases all three phenotypes are present.[128]

Over one hundred mutations in SCN5A have been linked to the syndrome in recent years (see [129] for references; also see www.fsm.it/cardmoc). Only a fraction of these mutations have been studied in expression systems and shown to result in loss of function due either to: 1) failure of the sodium channel to express; 2) a shift in the voltage- and time-dependence of sodium channel current (I_{Na}) activation, inactivation or reactivation; 3) entry of the sodium channel into an intermediate state of inactivation from which it recovers more slowly or 4) accelerated inactivation of the sodium channel. In *in vitro* expression systems, the premature inactivation of the sodium channel is sometimes observed at physiological temperatures, but not at room temperature [130]. Acceleration of I_{Na} inactivation was still more accentuated at higher than physiological temperatures, suggesting that the syndrome may be unmasked, and that patients with the Brugada syndrome may be at an increased risk, during a febrile state[130]. A number of Brugada patients displaying fever-induced polymorphic VT have been identified since the publication of this report[131-140].

Mutation in the *SCN5A* gene account for approximately 18-30% of Brugada syndrome cases. A higher incidence of *SCN5A* mutations has been reported in familial than in sporadic cases[141]. Of note, negative *SCN5A* results generally do not rule out causal gene mutations, since the promoter region, cryptic splicing mutations or presence of gross rearrangements are generally not part of routine investigation. A recent report by Hong et al. [142] provided the first report of a dysfunctional sodium channel created by an intronic mutation giving rise to cryptic splice site activation in SCN5A in a family with the Brugada syndrome. The deletion of fragments of segments 2 and 3 of Domain IV of SCN5A caused complete loss of function.

Bezzina and coworkers recently provided interesting evidence in support of the hypothesis that an SCN5A promoter polymorphism common in Asians modulates variability in cardiac conduction, and may contribute to the high prevalence of Brugada syndrome in the Asian population.[143] Sequencing of the SCN5A promoter identified a haplotype variant consisting of 6 polymorphisms in near-complete linkage disequilibrium that occurred at an allele frequency of 22% in Asian subjects and was absent in whites and blacks. The results of the study demonstrate that sodium channel transcription in the human heart may vary considerably among individuals and races and be associated with variable conduction velocity and arrhythmia susceptibility.

A second locus on chromosome 3, close to but distinct from SCN5A, has been linked to the syndrome [144] in a large pedigree in which the syndrome is associated with progressive conduction disease, a low sensitivity to procainamide, and a relatively good prognosis. The gene was recently identified as the Glycerol-3-Phosphate Dehydrogenase 1-Like Gene (GPD1L). A mutation in GPD1L has been shown to result in a partial reduction of I_{Na}.[145].

Knowledge thus far gained through genetic analysis suggests that identification of specific mutations may not be very helpful in formulating a diagnosis or providing a prognosis. There are no clear hotspots and mutations have been reported throughout the SCN5A gene. It is not clear whether some mutations are associated with a greater risk of arrhythmic events or sudden death. Genetic testing is recommended for support of the clinical diagnosis, for early detection of relatives at potential risk and particularly for the purpose of advancing research and consequently our understanding of genotype-phenotype relations.

Amplification of epicardial and transmural dispersion of repolarization secondary to the presence of genetic defects, pathophysiologic factors and pharmacologic influences, leads to accentuation of the J wave and eventually to loss of the action potential dome, giving rise to extrasystolic activity in the form of phase 2 reentry. Activation of I_{to} leads to a paradoxical prolongation of APD in canine ventricular tissues, [146] but to abbreviation of ventricular APD in species that normally exhibit brief action potentials (e.g., mouse and rat).[147] Pathophysiologic conditions (e.g., ischemia, metabolic inhibition) and some pharmacologic interventions (e.g., I_{Na} or I_{Ca} blockers or $I_{K\text{-}ATP}$, I_{to}, I_{Kr} or I_{Ks} activators) can lead to marked abbreviation of APD in canine and feline[148] ventricular cells where I_{to} is prominent. Under these conditions, canine ventricular epicardium exhibits an all-or-none repolarization as a result of the shift in the balance of currents flowing at the end of phase 1 of the action potential. All-or-none repolarization of the action potential occurs when phase 1 reaches approximately -30 mV. This leads to loss of the action potential dome as the outward currents overwhelm the inward currents. Loss of the dome generally occurs at some epicardial sites but not others, resulting in the development of a marked dispersion of repolarization within the epicardium as well as transmurally, between epicardium and endocardium. Propagation of the action potential dome from the epicardial site at which it is maintained to sites at which it is abolished can cause local re-excitation of the preparation. This mechanism, termed phase 2 reentry, produces extrasystolic beats capable of initiating circus movement reentry.[149] Phase 2 reentry has been shown to occur when right ventricular epicardium is exposed to: 1) K+ channel openers such as pinacidil;[150] 2) sodium channel blockers such as flecainide;[151] 3) increased [Ca2+]o;[152] 4) calcium channel blockers such as verapamil; 5) metabolic inhibition;[153] and 6) simulated ischemia.[149]

Exaggerated or otherwise abnormal J waves have long been linked to idiopathic ventricular fibrillation as well as to the Brugada syndrome.[124, 154-158] The Brugada syndrome is characterized by exaggerated J wave that manifests as an ST segment elevation in the right precordial leads.[124] A number of studies have highlighted the similarities between the conditions that predispose to phase 2 reentry and those that attend the appearance of the Brugada syndrome. Loss of the action potential dome in epicardium, but not endocardium generates a transmural current that

manifests on the ECG as an ST segment elevation, similar to that encountered in patients with the Brugada syndrome.[107, 153, 159] Evidence in support of a phase 2 reentrant mechanism in humans was recently provided by Thomsen et al.[160, 161]

Parasympathetic agonists like acetylcholine facilitate loss of the action potential dome [162] by suppressing I_{Ca} and/or augmenting potassium current. β-adrenergic agonists restore the dome by augmenting I_{Ca}. Sodium channel blockers also facilitate loss of the canine right ventricular action potential dome via a negative shift in the voltage at which phase 1 begins.[151, 163] These findings are consistent with accentuation of ST segment elevation in patients with the Brugada syndrome following vagal maneuvers or Class I antiarrhythmic agents as well as normalization of the ST segment elevation following β adrenergic agents and phosphodiesterase III inhibitors [107, 164, 165]. Loss of the action potential dome is more readily induced in right vs. left canine ventricular epicardium [10, 153, 159] because of the more prominent I_{to}-mediated phase 1 in action potentials in this region of the heart. As previously noted, this distinction is believed to be the basis for why the Brugada syndrome is a right ventricular disease.

In the past, much of the focus was been on the ability of a reduction in sodium channel current to unmask the Brugada syndrome and crate and arrhythmogenic substrate. A recent report shows that a combination of I_{Na} and I_{Ca} block is more effective than I_{Na} inhibition alone in precipitating the Brugada syndrome in the arterially-perfused wedge preparation. [166]

The ST segment elevation associated with the Brugada syndrome has be attributed to: 1) conduction delay in the right ventricular epicardial free wall in the region of the outflow tract (RVOT)[167] and/or 2) accentuation of the right ventricular epicardial action potential that may lead to loss of the action potential dome.[168] The cellular mechanisms thought to be responsible for the development of the Brugada phenotype via hypothesis 2 is schematically illustrated in **Fig. 2.** [169, 170].

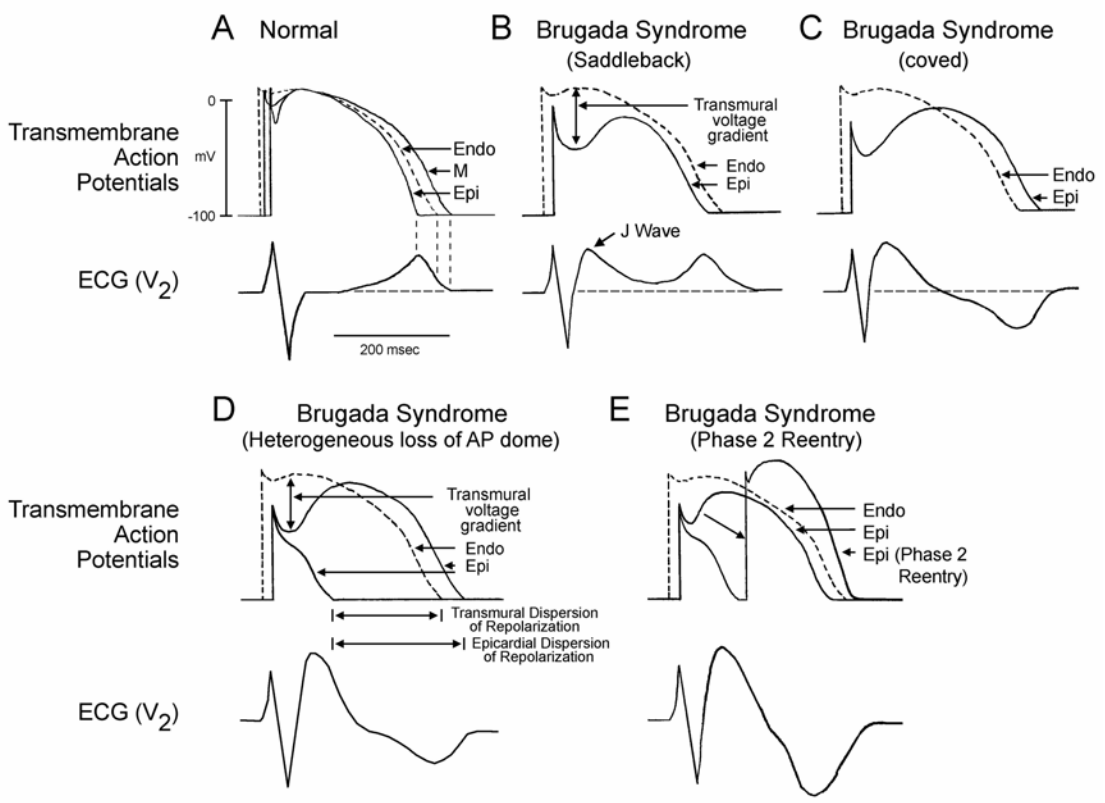

Figure 2. Schematic representation of right ventricular epicardial action potential changes proposed to underlie the electrocardiographic manifestation of the Brugada syndrome. Modified from [169], with permission.

The ST segment is usually isoelectric because of the absence of transmural voltage gradients at the level of the action potential plateau (**Fig. 2A**). Accentuation of the right ventricular notch under pathophysiologic conditions leads to exaggeration of transmural voltage gradients and thus to accentuation of the J wave or to J point elevation. When epicardial repolarization precedes repolarization of the cells in the M and endocardial regions the T wave remains positive. This results in a saddleback configuration of the repolarization waves (**Fig. 2B**). Further accentuation of the notch may be accompanied by a prolongation of the epicardial action potential such that the direction of repolarization across the right ventricular wall and transmural voltage gradients are reversed, leading to the development of a coved-type ST segment elevation and inversion of the T wave (**Fig. 2C)**, typically observed in the ECG of Brugada patients. A delay in epicardial activation may also contribute to inversion of the T wave. The downsloping ST segment elevation observed

in the experimental wedge models often appears as an R', suggesting that the appearance of a right bundle branch block (RBBB) morphology in Brugada patients may be due at least in part to early repolarization of right ventricular (RV) epicardium, rather than major impulse conduction block in the right bundle.

Gussak and coworkers pointed out that a majority of RBBB-like morphologies encountered in cases of Brugada syndrome do not fit the criteria for RBBB [171]. Moreover, attempts by Miyazaki and coworkers to record delayed activation of the RV in Brugada patients met with failure [164].

It is important to point out that although the typical Brugada morphology is present in **Fig. 2B and C**, an arrhythmogenic substrate is absent. The arrhythmogenic substrate is thought to develop when a further shift in the balance of current leads to loss of the action potential dome at some epicardial sites but not others (**Fig. 2D)**. Loss of the action potential dome in epicardium but not endocardium results in the development of a marked transmural dispersion of repolarization and refractoriness, responsible for the development of a vulnerable window during which a premature impulse or extrasystole can induce a reentrant arrhythmia. Conduction of the action potential dome from sites at which it is maintained to sites at which it is lost causes local re-excitation via a phase 2 reentry mechanism, leading to the development of a very closely-coupled extrasystole, which captures the vulnerable window across the wall, thus triggering a circus movement reentry in the form of VT/VF (**Fig. 2E**)[149, 172]. The phase 2 reentrant beat fuses with the T wave of the basic response, thus accentuating the negative T wave. This morphology is often observed in the clinic preceding the onset of polymorphic VT.

Studies involving the arterially-perfused right ventricular wedge preparation provide evidence in support of these hypotheses. [172] Aiba et al.[173] used a high resolution optical mapping system that allows simultaneous recording of transmembrane action potentials from 256 sites along the transmural surface of the arterially-perfused canine right-ventricular wedge preparation to demonstrate that a steep repolarization gradient between the region at which the dome is lost and the region at which it is maintained is essential for the development of a closely coupled phase 2 reentrant extrasystole. This study also showed that reentry initially rotates in the epicardium and gradually shifts to a transmural orientation, responsible for nonsustained polymorphic VT or VF.

Kurita et al. placed monophasic action potential (MAP) electrodes on the epicardial and endocardial surfaces of the right ventricular outflow tract (RVOT) in patients with the Brugada syndrome and demonstrated an accentuated notch in the epicardial response, thus providing support for this mechanism in humans.[174, 175]

Thus, accentuation of the right ventricular epicardial action potential notch underlies the ST segment elevation. Eventual loss of the dome of the right ventricular epicardial action potential

further exaggerates ST segment elevation. A vulnerable window is created both within epicardium, as well as transmurally, which serves as the substrate for the development of reentry (**Fig. 3**).

Phase 2 reentry provides the extrasystole that serves as the trigger that precipitates episodes of ventricular tachycardia and fibrillation in the Brugada syndrome. Evidence in support of this hypothesis was recently provided in an arterially-perfused canine right ventricular experimental model of the Brugada syndrome.[172] The VT and VF generated in these preparations is usually polymorphic, resembling a rapid form of Torsade de Pointes (TdP). This activity is likely related to the migrating spiral wave shown to generate a pattern resembling a polymorphic VT.[176, 177]

Role of TDR in Channelopathy-mediated Sudden Death

The three inherited sudden death syndromes discussed thus far differ with respect to the characteristics of the QT interval (**Figure 4**). In the long QT syndrome, QT interval increases as a function of disease or drug concentration. In the Brugada syndrome it remains largely unchanged and in the short QT syndrome QT interval decreases as a function of disease of drug. What the three syndromes have in common is an amplification of TDR, which results in the development of TdP when dispersion reaches the threshold for reentry. It is noteworthy that the threshold for reentry decreases as APD and refractoriness are reduced.

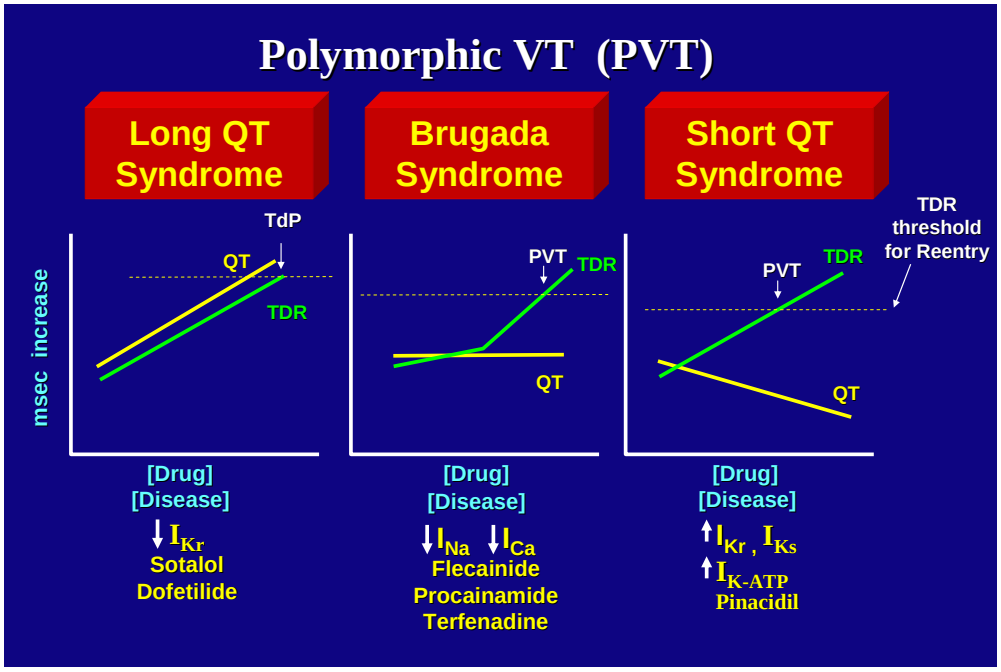

Figure 4. The role of transmural dispersion of repolarization (TDR) in Channelopathy-induced Sudden Death. In the long QT syndrome, QT increases as a function of disease or drug concentration. In the Brugada syndrome it remains largely unchanged and in the short QT syndrome QT interval decreases as a function of disease of drug. The three syndromes have in common the ability to amplify TDR, which results in the development of TdP when dispersion reaches the threshold for reentry. The threshold for reentry decreases as APD and refractoriness are reduced. From [185]. With permission.

Does TDR Play a Role in Catecholaminergic Polymorphic VT

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is another inherited sudden death syndrome. CPVT is a rare, autosomal dominant or recessive inherited disorder, predominantly affecting children or adolescents with structurally normal hearts. It is characterized by bidirectional ventricular tachycardia (BiVT), polymorphic VT (PVT), and a high risk of sudden cardiac death (30-50% by the age of 20 to 30 years).[178,179] Recent molecular genetic studies have identified mutations in genes encoding for the cardiac ryanodine receptor 2 (RyR2) or calsequestrin 2 (CASQ2) in patients with this phenotype.[180-183] Mutations in RyR2 cause autosomal dominant CPVT, whereas mutations in CASQ2 are responsible for either an autosomal recessive or dominant form of CPVT.

Several lines of evidence have implicated delayed afterdepolarization (DAD)-induced triggered activity (TA) in the development of monomorphic or bidirectional VT in patients with this syndrome. The cellular mechanisms underlying the various ECG phenotypes, and the transition of monomorphic VT to polymorphic VT or VF, were recently elucidated with the help of the coronary-perfused left ventricular wedge preparation.[184] The wedge was exposed to low dose caffeine to mimic the defective calcium homeostasis encountered under conditions that predispose to CPVT. The combination of isoproterenol and caffeine led to the development of DAD-induced triggered activity arising from the epicardium, endocardium or M region. Migration of the source of ectopic activity was responsible for the transition from monomorphic to slow polymorphic VT. Alternation of epicardial and endocardial source of ectopic activity gave rise to a bidirectional VT. The triggered activity-induced monomorphic, bidirectional and slow polymorphic VT would be expected to be hemodynamically well tolerated because of the relatively slow rate of these rhythms and are unlikely to be the cause of sudden death in these syndromes.

Epicardial ectopy and VT were associated with an increased Tpeak-Tend interval and transmural dispersion of repolarization due to reversal of the normal transmural activation sequence. The increase in TDR was sufficient to create the substrate for reentry and programmed electrical stimulation induced a rapid polymorphic VT that would be expected to lead hemodynamic compromise.[184] Thus, even in a syndrome in which arrhythmogenesis is traditionally ascribed to triggered activity, sudden death may be due to amplification of TDR, giving rise to reentrant VT/VF.

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