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Amplification of spatial dispersion of repolarization underlies sudden cardiac death associated with catecholaminergic polymorphic VT, long QT, short QT and Brugada syndromes

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Abstract

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This review examines the hypothesis that amplification of spatial dispersion of repolarization in the form of transmural dispersion of repolarization (TDR) 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. 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 because of selective abbreviation of the APD of right ventricular 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 aetiologies, but which share a common final pathway in causing sudden death.

Keywords

arrhythmia; electrocardiogram; electrophysiology; ventricle

Introduction

Heterogeneities of ventricular repolarization have long been implicated in arrhythmogenesis. This review presents evidence in support of the hypothesis that amplification of spatial dispersion of repolarization in the form of transmural dispersion of repolarization (TDR) underlies 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). In the long QT syndrome (LQTS), 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 because of preferential abbreviation of the APD of right ventricular (RV) epicardium. Reports published over the past couple of years, indicate that preferential abbreviation of APD of either

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endocardium or epicardium is responsible for amplification of TDR in the short QT syndrome (SQTS). Finally, in catecholaminergic polymorphic VT, the reversal of the direction of activation of the ventricular wall appears to be responsible for the increase in TDR.

Long QT syndrome

The LQTSs are phenotypically and genotypically diverse, but have in common the appearance of long QT interval in the electrocardiogram (ECG), an atypical polymorphic VT known as torsade de pointes (TdP), and, in many but not all cases, a relatively high risk for sudden cardiac death [1-3]. Congenital LQTS is subdivided into eight genotypes distinguished by mutations in at least seven different ion genes and a structural anchoring protein located on chromosomes 3, 4, 6, 7, 11, 17 and 21 (Table 1) [4-9]. Timothy syndrome, also referred to 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 hypoglycaemia, cognitive abnormalities and autism. Timothy syndrome has been linked to loss of voltage-dependent inactivation caused by mutations in $Ca_v1.2$, the gene that encodes for an a subunit of the calcium channel [10].

Two patterns of inheritance have been identified: (i) a rare autosomal recessive disease associated with deafness (Jervell and Lang-Nielsen), caused by two genes that encode for the slowly activating delayed rectifier potassium channel (KCNQ1 and KCNE1); and (ii) a much more common autosomal dominant form known as the Romano-Ward syndrome, caused by mutations in eight 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) and CACNA1C ($Ca_v1.2$, LQT8, Timothy syndrome). Five of eight genes encode for cardiac potassium channels, one for the cardiac sodium channel (SCN5A), one for the 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 [11]. 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 (implantable cardioverter defibrillator) and/or cardiac sympathetic denervation may be therapeutic alternatives [12,13].

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 [14] 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 [15-19]. The acquired form of the disease is far more prevalent than the congenital form, and in some cases may have a genetic predisposition.

Amplification of spatial dispersion of repolarization within the ventricular myocardium has been identified as the principal arrhythmogenic substrate in both acquired and congenital LQTS. The accentuation of spatial dispersion, typically secondary to an increase of transmural, trans-septal or apico-basal dispersion of repolarization, and the development of early afterdepolarization (EAD)-induced triggered activity (TA) underlie the substrate and trigger for the development of TdP arrhythmias observed under LQTS conditions [20,21]. Models of the LQT1, LQT2, and LQT3 forms of the LQTS have been developed using the canine arterially perfused left ventricular wedge preparation [22]. These models suggest that in these three forms of LQTS, preferential prolongation of the M-cell APD leads to an increase in the QT interval

as well as an increase in TDR, which contributes to the development of spontaneous as well as stimulation-induced TdP [23-25].

The unique characteristics of the M cells are at the heart the LQTS. The hallmark of the M cell is the ability of its action potential to prolong more than that of epicardium or endocardium with slowing of rate. In the early 1990s, the M cells became the focus of intense investigation after their identification and characterization in the ventricular wall [26-28]. M-cell distribution in ventricular myocardium has been investigated in greatest detail in the canine left ventricle. M cells with the longest APD are typically found in the deep subendocardium to midmyocardium in the anterior wall. M cells have also been identified in the deep layers of papillary muscles, trabeculae, and interventricular septum [29]. Myocytes enzymatically dissociated from the different layers of the left ventricular wall typically display APD values at 90% repolarization (APD_{90}) that differ by more than 200 ms at slow rates of stimulation (basic cycle lengths ≥ 2000 ms). In the intact ventricular wall, this disparity in APD_{90} is less pronounced (25- 55 ms) because of electrotonic interaction amongst the different cell types. The transmural increase in APD is relatively gradual, except between the epicardium and subepicardium where there is often a sharp increase in APD. This has been shown to be due to an increase in tissue resistivity in this region [30], which may be related to the sharp transition in cell orientation in this region as well as to reduced expression of connexin 43 [31,32], which is principally responsible for intracellular communication in ventricular myocardium. The degree of electrotonic coupling together with the intrinsic differences APD contribute to TDR in the ventricular myocardium. The prolonged APD of M cell has been shown to be due to a smaller I_{Ks} and a larger late I_{Na} [33,34] and sodium-calcium exchange current (I_{Na-Ca}) [35] compared with epicardial and endocardial cells. These differences contribute to a reduced repolarizing current during phases 2 and 3 of the M-cell action potential.

These ionic distinctions sensitize the M cells to a variety of pharmacological agents. 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.

Differences in the time course of repolarization of the three predominant myocardial cell types have been shown to contribute prominently to the inscription of the T wave of the ECG. Voltage gradients developing as a result of the different time course of repolarization of phases 2 and 3 in the three cell types give rise to opposing voltage gradients on either side of the M region, which are in large part responsible for the inscription of the T wave [36]. In the case of an upright T wave, the epicardial response is the earliest to repolarize and the M cell action potential is the latest. Full repolarization of the epicardial action potential coincides with the peak of the T wave and repolarization of the M cells is coincident with the end of the T wave. The duration of the M cell action potential therefore determines the QT interval, whereas the duration of the epicardial action potential determines the QTpeak interval.

Tpeak-Tend interval has been shown to provide an index of TDR [27]. The available data suggest that Tpeak-Tend measurements are generally limited to precordial leads as these leads more accurately reflect TDR. Recent studies have also provided guidelines for the estimation of TDR in the case of more complex T waves, including negative, biphasic and triphasic T waves [37]. In these cases, the interval from the nadir of the first component of the T wave to the end of the T wave provides an accurate electrocardiographic approximation of TDR.

Whilst 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 achieved. Lubinski et al. [38] demonstrated that this interval is increased in patients with congenital LQTS. 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 [39-44]. Takenaka et al. [43] recently demonstrated exercise-induced accentuation of the Tpeak-Tend interval in LQT1 patients, but not LQT2. These observations coupled with those of Schwartz et al. [45] 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 a valuable index to predict TdP in patients with LQTS was provided by Yamaguchi et al. [46]. These authors concluded that Tpeak-Tend is more valuable than QTc and QT dispersion as a predictor of TdP in patients with acquired LQTS. Shimizu et al. [42] demonstrated that Tpeak-Tend, but not QTc, predicted sudden cardiac death in patients with hypertrophic cardiomyopathy. Most recently, Watanabe et al. [44] demonstrated that prolonged Tpeak-Tend is associated with inducibility as well as spontaneous development of VT in high risk patients with organic heart disease.

Although further studies are needed to evaluate the utility of these non-invasive indices of electrical heterogeneity and their prognostic value in the assignment of arrhythmic risk, evidence is accumulating in support of the hypothesis that TDR rather than QT prolongation underlies the substrate responsible for the development of TdP [20,47-50].

Available data point to the following hypothesis as the basis for LQTS-related TdP (Fig. 1). The hypothesis presumes the presence of electrical heterogeneity in the form of TDR 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 leading to a reduction in I_{Kr} or augmentation of late I_{Na} 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 TDR, thus creating a vulnerable window for the development of reentry. The reduction in net repolarizing current also predisposes to the development of EAD-induced TA in M and Purkinje cells, which provide the extrasystole that triggers TdP when it falls within the vulnerable period. β -Adrenergic agonists further amplify trans-mural heterogeneity (transiently) in the case of I_{Kr} or I_{Ks} block, but reduce it in the case of I_{Na} agonists [25,51].

Not all agents that prolong the QT interval increase TDR. Amiodarone, a potent anti-arrhythmic agent used in the management of both atrial and ventricular arrhythmias, is rarely associated with TdP. Chronic administration of amiodarone produces a greater prolongation of APD in epicardium and endocardium, but less of an increase, or even a decrease at slow rates, in the M region, thereby reducing TDR [8]. 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 four of eight dogs with the highest spatial dispersion of repolarization (105 ± 20 ms) [9]. Sodium pentobarbital is another agent that prolongs the QT interval but reduces TDR. Pentobarbital has been shown to produce a dose-dependent prolongation of the QT interval, accompanied by a reduction in TDR from 51 to 27 ms [10]. TdP is never seen 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.

Another agent that blocks both inward and outward currents is cisapride. Cisapride produces a biphasic dose-dependent prolongation of the QT interval. A parallel biphasic dose-response relationship is seen for TDR, peaking at $0.2 \mu\text{mol L}^{-1}$, and it is only at this concentration that TdP is observed. At higher concentrations of cisapride, QT is further prolonged but TDR was diminished, and TdP could no longer be induced [11]. This finding suggests that the spatial dispersion of repolarization is more important than the prolongation of the QT interval in determining the substrate for TdP.

Chromanol 293B, an I_{Ks} blocker, is another example of an agent that increases QT without augmenting TDR. Chromanol 293B prolongs APD of the three cell types homogeneously, neither increasing TDR nor widening the T wave. TdP is never observed under these conditions. This picture changes very quickly in the presence of β -adrenergic stimulation. Isoprenaline abbreviates the APD of epicardial and endocardial cells but not that of the M cell, resulting in a marked accentuation of TDR [12]. TdP develops under these conditions. These findings have advanced our understanding of why long QT patients, LQT1 in particular, are so sensitive to sympathetic influences, and 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 the increase in spatial dispersion of repolarization that usually, but not always, accompanies the prolongation of the QT interval.

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 [52]. The ECG sign of the Brugada syndrome is dynamic and often concealed, but can be unmasked by potent sodium channel blockers such as ajmaline, flecainide, procainamide, disopyramide, propafenone and pilsicainide [53-55]. The arrhythmogenic substrate responsible for the development of extrasystoles and polymorphic VT in the Brugada syndrome is thought to be secondary to amplification of heterogeneities intrinsic to the early phases (phase 1-mediated notch) of the action potential of cells residing in different layers of the RV wall of the heart (Fig. 2). Rebalancing of the currents active at the end of phase 1, is thought to underlie the accentuation of the action potential notch in RV epicardium, which is responsible for the augmented J wave and ST segment elevation associated with the Brugada syndrome (see [56] for references). The ST segment is normally close to isoelectric due to the absence of major transmural voltage gradients at the level of the action potential plateau. Accentuation of the RV action potential notch under pathophysiological conditions leads to exaggeration of transmural voltage gradients and thus to accentuation of the J wave or to an elevation of the J point. If the epicardial action potential continues to repolarize before that of endocardium, the T wave remains positive, giving rise to a saddleback configuration of the ST segment elevation. Further accentuation of the notch is accompanied by a prolongation of the epicardial action potential causing it to repolarize after endocardium, thus leading to inversion of the T wave.

Experiments performed using the coronary-per-fused canine RV wedge preparation suggest that the accentuated J wave (down-sloping ST segment elevation), which often appears as an R' resembling right bundle branch block, in Brugada patients may be due in large part to early repolarization of RV epicardium, rather than major delays in impulse conduction in the right bundle [57], although right ventricular outflow tract (RVOT) conduction delays may also contribute to the Brugada phenotype [58]. Despite the appearance of a typical Brugada sign, accentuation of the RV epicardial AP notch alone does not give rise to an arrhythmogenic substrate. The arrhythmogenic substrate may develop with a further shift in the balance of current leading to loss of the action potential dome at some epicardial sites but not others. A marked TDR develops as a consequence, creating a vulnerable window, which when captured by a premature extrasystole can trigger a reentrant arrhythmia. Because loss of the action potential dome in epicardium is generally heterogeneous, epicardial dispersion of repolarization develops as well. 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 phase 2 reentry, leading to the development of a closely coupled extrasystole capable of capturing the vulnerable window across the ventricular wall, thus triggering a circus movement reentry in the form of VT/VF [59,60]. Support for these hypotheses derives from experiments involving the arterially

perfused RV wedge preparation [59] and from recent studies in which monophasic action potential electrodes were positioned on the epicardial and endocardial surfaces of the RVOT in patients with the Brugada syndrome [61,62].

Short QT syndrome

The SQTS was first proposed as a clinical entity by Gussak et al. in 2000 [63]. SQTS is an inherited syndrome characterized by a $QT_c \leq 300$ ms and high incidence of VT/VF in infants, children and young adults [64]. The familial nature of this sudden death syndrome was highlighted by Gaita et al. in 2003 [65]. The first genetic defect responsible for the SQTS (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} [66]. A second gene was recently reported by Bellocq et al. (SQTS2) [67]. A missense mutation in KCNQ1 (KvLQT1) caused a gain of function in I_{Ks} . A third gene (SQTS3), 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. SQTS3 is associated with QT_c intervals, < 330 ms, not quite as short as SQTS1 and SQTS2.

The SQTS 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 SQTS have provided evidence in support of the hypothesis that an increase in outward repolarizing current can preferentially abbreviate endocardial/M cell thus increasing TDR and creating the substrate for reentry [68]. The potassium channel opener pinacidil used in this study caused a heterogeneous abbreviation of APD amongst 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 isoprenaline, leading to easier induction and more persistent VT/VF. It is noteworthy that an increase of TDR to values >55 ms was associated with inducibility of VT/VF. In LQTS models, a TDR of >90 ms 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 [68].

The role of TDR in channelopathy-induced sudden death

The three inherited sudden death syndromes discussed thus far differ with respect to the behaviour of the QT interval (Fig. 3). In the LQTS, QT increases as a function of disease or drug concentration. In the Brugada syndrome it remains largely unchanged and in the SQTS QT interval decreases as a function of disease or drug. What these three syndromes have in common is an amplification of TDR, which results in the development of TdP when dispersion reaches the threshold for reentry. Of note is the fact that the threshold for reentry decreases as APD and refractoriness are reduced.

Catecholaminergic polymorphic VT

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, polymorphic VT, and a high risk of sudden cardiac death (30-50% by the age of 20-30 years) [69,70]. 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 [71-74]. 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 point to delayed afterdepolarization (DAD)-induced TA as the mechanism underlying 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 [75]. The wedge was exposed to low dose caffeine to mimic the defective calcium homeostasis encountered under conditions that predispose to CPVT. The combination of isoprenaline and caffeine led to the development of DAD-induced TA 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 TA-induced monomorphic, bidirectional and slow polymorphic VT would be expected to be haemodynamically 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 TDR 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 haemodynamic compromise [75]. Thus, even in a syndrome in which arrhythmogenesis is traditionally ascribed to TA, sudden death may be due to amplification of TDR, giving rise to reentrant VT/VF.

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Fig. 1.
Proposed cellular mechanism for the development of torsade de pointes in the long QT syndromes.

Fig. 2.

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 with permission from Antzelevitch [76].

Fig. 3.

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 or 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.

Table 1

Genetic disorders caused by ion channelopathies

Ventricular	Rhythm	Inheritance	Locus	Ion channel	Gene
Long QT syndrome (RW)	TdP	AD			
LQT1			11p15	IKs	KCNQ1, KvLQT1
LQT2			7q35	IKr	KCNH2, HERG
LQT3			3p21	INa	Nav1.5, SCN5A
LQT4			4q25		ANKB, ANK2
LQT5			21q22	IKs	KCNE1, minK
LQT6			21q22	IKr	KCNE2, MiRP1
LQT7	(Andersen-Tawil syndrome)		17q23	IK1	KCNJ2, Kir 2.1
LQT8	(Timothy syndrome)		6q8A	ICa-L	Cav1.2, CACNA1C
Long QT syndrome (JLN)	TdP	AR	11p15	IKs	KCNQ1, KvLQT1
			21q22	IKs	KCNE1, minK
Brugada syndrome	VT/VF	AD	3p21	INa	Nav1.5, SCN5A
			3p22-25		
Short QT syndrome					
SQT1	VT/VF	AD	7q35	IKr	KCNH2, HERG
SQT2		AD	11p15	IKs	KCNQ1, KvLQT1
SQT3		AD	17q23.1-24.2	IK1	KCNJ2, Kir2.1
Catecholaminergic VT					
CPVT1	VT	AD	1q42-43		RyR2
CPVT2	VT	AR	1p13-21		CASQ2

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.