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Heterogeneity and Cardiac Arrhythmias: An Overview

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Abstract

This lecture 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 (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, 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. These syndromes, however, share a common final pathway in their predisposition to sudden cardiac death.

Keywords

Long QT Syndrome; Short QT Syndrome; Brugada Syndrome; Polymorphic Ventricular Tachycardia; Electrophysiology

It was 17 years ago that I came before the Cardiac Electrophysiology Society with the recommendation to name the keynote lecture of the Society the Gordon K. Moe Lecture in memory of Gordon K. Moe, who had passed away earlier that year. The year was 1989. It is a distinct honor and privilege to be invited to present this lecture and to have the opportunity to remember Gordon to all of you and to present some of what we have done to further his seminal contributions to our field.

Dr. Moe was an energetic and charismatic friend and scientist with a vision of the future unique among men. Among his team's many contributions to the field of cardiac electrophysiology and arrhythmias were studies demonstrating that dispersion of recovery of excitability in the atria and ventricles of the heart predispose to the development of both atrial and ventricular arrhythmias.^{1, 2} The delineation of electrical heterogeneities in the atria led to their pioneering theories regarding the mechanism responsible for atrial fibrillation.³

In this lecture I will review some of our work of recent years that has served to extend and build on this theme. My focus will be on evidence in support of the hypothesis that amplification of spatial dispersion of repolarization, particularly 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

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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 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 endocardium or epicardium is responsible for amplification of TDR in the short QT syndrome. 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.

The Long QT Syndrome

The best studied of the channelopathies are the long QT syndromes (LQTS). They are phenotypically and genotypically diverse, but have in common the appearance of a long QT interval in the ECG, an atypical polymorphic ventricular tachycardia known as Torsade de Pointes (TdP), and, in many but not all cases, a relatively high risk for sudden cardiac death.^{4–6} Ten genotypes characterize the congenital LQT syndromes. They are distinguished by mutations in at least eight different ion channel genes, a structural anchoring protein and a caveolin protein located on chromosomes 3, 4, 6, 7, 11, 17 and 21 (Table 1).^{7–12}

Andersen–Tawil syndrome,⁹ also referred to as LQT7, is characterized by skeletal muscle periodic paralysis, frequent ectopy, but relatively rare episodes of TdP, secondary to loss of function mutations in *KCNJ2*, which encodes Kir2.1, the channel conducting the inward rectifier current, I_{K1} . 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 *CACNA1C*, the gene that encodes $Ca_v1.2$, the α subunit of the calcium channel.¹³ 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. Caveolin-3 spans the plasma membrane twice, forming a hairpin structure on the surface, and is the main constituent of caveolae, small invaginations in the plasma membrane. Mutations in *CAV3* and *SCNB4* both produce a gain of function in late I_{Na} , causing an LQT3-like phenotype.^{14, 15}

LQTS shows both autosomal recessive and autosomal dominant patterns of inheritance: 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 as the Romano-Ward syndrome, caused by mutations in 10 different genes (Table 1). Eight of the 10 genes encode for cardiac potassium channels.

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 potential¹⁶ or QT prolongation secondary to cardiomyopathies including dilated or hypertrophic cardiomyopathy, as well as to abnormal QT prolongation associated with bradycardia or electrolyte imbalance.^{17–21} The acquired form of the disease is far more prevalent than the congenital form, and in some cases may have a genetic predisposition.²²

Accentuation of spatial dispersion of repolarization within the ventricular myocardium has been identified as the principal arrhythmogenic substrate in both acquired and congenital LQTS. The amplification of spatial dispersion of refractoriness can take the form of an increase of transmural, trans-septal or apico-basal dispersion of repolarization. This exaggerated

intrinsic heterogeneity together with early and delayed afterdepolarization (EAD and DAD)-induced triggered activity, both caused by reduction in net repolarizing current, underlie the substrate and trigger for the development of Torsade de Pointes arrhythmias observed under LQTS conditions (Figure 1).^{23, 24} Models of the LQT1, LQT2, and LQT3 forms of the long QT syndrome have been developed using the canine arterially perfused left ventricular wedge preparation.²⁵ 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 transmural dispersion of repolarization (TDR), which contributes to the development of spontaneous as well as stimulation-induced Torsade de Pointes (TdP) (Figure 1).^{26–30}

The **M Cell**, **M**asonic **M**idmyocardial **M**oe Cell, discovered in the early 1990's, was named in memory of Gordon K. Moe.^{31–33} 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 or in response to agents that prolong APD. M cells with the longest action potential duration 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.³⁴ Myocytes enzymatically dissociated from the different layers of the left ventricular wall typically display APD values at 90 percent repolarization (APD₉₀) that differ by more than 200 msec at slow rates of stimulation (basic cycle lengths $\geq$ 2000 msec). In the intact ventricular wall, this dispersion of APD₉₀ is less pronounced (25–55 msec) because of electrotonic interaction among the different cell types. The transmural increase in APD from epi- to endocardium 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 region³⁵, which may be related to the sharp transition in cell orientation in this region as well as to reduced expression of connexin 43,^{36, 37} which is principally responsible for intracellular communication in ventricular myocardium. The degree of electrotonic coupling together with the intrinsic differences APD contribute to transmural dispersion of repolarization in the ventricular myocardium.³⁸ The prolonged APD of the M cell has been shown to be due to a smaller slowly activating delayed rectifier current (I_{Ks}) and a larger late I_{Na} ^{39, 40} and sodium-calcium exchange current (I_{Na-Ca})⁴¹ compared to epicardial and endocardial cells. These ionic distinctions sensitize the M cells to a variety of pharmacological agents. Agents that block the rapidly activating delayed rectifier current (I_{Kr}), I_{Ks} or that increase calcium channel current (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.

Transmural electrical heterogeneity also underlies the inscription of the repolarization waves of the electrocardiogram (ECG). Differences in the time course of repolarization of the three predominant myocardial cell types 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 part responsible for the inscription of the T wave.⁴² 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.

The interval between the peak and end of the T wave (Tpeak–Tend interval) in precordial ECG leads has been suggested to provide an index of transmural dispersion of repolarization.³² 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.⁴³ 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 transmural dispersion of repolarization.

Although Tpeak-Tend interval is unlikely to provide an absolute measure of transmural dispersion *in vivo*, changes in this parameter are thought to reflect changes in spatial dispersion of repolarization and thus may be prognostic of arrhythmic risk under a variety of conditions.^{44–49} Takenaka et al. recently demonstrated exercise-induced accentuation of the Tpeak-Tend interval in LQT1 patients, but not LQT2.⁴⁸ These observations coupled with those of Schwartz et al.⁵⁰, 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.⁵¹ 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 cardiomyopathy.⁴⁷ Most recently, Watanabe et al. demonstrated that prolonged Tpeak-Tend is associated with inducibility as well as spontaneous development of ventricular tachycardia (VT) in high risk patients with organic heart disease.⁴⁹

Evidence is accumulating in support of the hypothesis that TDR rather than QT prolongation underlies the principal substrate for the development of TdP.^{23, 52–55} Our working hypothesis for the development of LQTS-related TdP presumes the presence of electrical heterogeneity in the form of transmural 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} (Figure 1). 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 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.^{28, 56}

Although agents that block I_{Kr} and which increase late I_{Na} clearly augment TDR, not all agents that prolong the QT interval increase TDR. Amiodarone, a potent antiarrhythmic agent used in the management of both atrial and ventricular arrhythmias, is rarely associated with TdP. Chronic administration of amiodarone produces a greater prolongation of APD in epicardium and endocardium, but less of an increase, or even a decrease at slow rates, in the M region, thereby reducing TDR.⁵⁷ 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 with the highest spatial dispersion of repolarization (105 ± 20 ms).⁵⁸

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.⁵⁹ TdP is not observed under these conditions, nor can it be induced with programmed electrical 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 develop. Cisapride is another agent that blocks both inward and outward currents. In the canine left ventricular wedge preparation, cisapride produces a biphasic dose-dependent prolongation of the QT interval and TDR. TDR peaks at

0.2 μM , and it is only at this concentration that TdP is observed. Higher concentrations of cisapride lead to an abbreviation of TDR and elimination of TdP, even though QT is further prolonged.⁶⁰ 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.

Block of I_{Ks} with chromanol 293B also 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 never observed under these conditions. The addition of β adrenergic agonist such as isoproterenol, however, abbreviates the APD of epicardial and endocardial cells but not that of the M cell, resulting in a marked accentuation of TDR and the development of TdP.²⁸ These findings have provided insight into 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 elevated ST segment or J wave appearing in the right precordial leads (V1–V3), often followed by a negative T wave. First described in 1992, the syndrome is generally associated with a high incidence of sudden cardiac death secondary to a rapid polymorphic VT or VF.⁶¹ These ECG characteristics of the Brugada syndrome are dynamic and often concealed, but can be unmasked by potent sodium channel blockers such as ajmaline, flecainide, procainamide, disopyramide, propafenone and pilsicainide.^{62–64}

The sensitivity to sodium channel blockers is consistent with the findings that in at least 15% of Brugada Syndrome (BrS) probands the syndrome is associated with mutations in *SCN5A*, the gene that encodes for the α subunit of the cardiac sodium channel.⁶⁵ Over one hundred mutations in *SCN5A* have been linked to the syndrome in recent years (see 66 for references; also see <http://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. Mutations in the *SCN5A* gene account for approximately 15% of Brugada syndrome probands. A higher incidence of *SCN5A* mutations has been reported in familial than in sporadic cases⁶⁷. 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.⁶⁸ 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 co-workers 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.⁶⁹ 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 recently been linked to the syndrome⁷⁰ 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 reduction of I_{Na} .⁷¹

The third and fourth genes associated with the Brugada syndrome encode the $\alpha 1$ (CACNA1C) and β (CACNB2b) subunits of the L-type cardiac calcium channel. Mutations in the α and β subunits of the calcium channel also lead to a shorter than normal QT interval, in some cases creating a new clinical entity consisting of a combined Brugada/Short QT syndrome.⁷²

The development of extrasystoles and polymorphic VT in the Brugada syndrome has also been shown 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 right ventricular wall of the heart (Figure 2). Rebalancing of the currents active at the end of phase 1, is thought to underlie the accentuation of the action potential notch in right ventricular epicardium, which is responsible for the augmented J wave and ST segment elevation associated with the Brugada syndrome (see 73, 74 for references). Under physiologic conditions, the ST segment isoelectric due to the absence of major transmural voltage gradients at the level of the action potential plateau. Accentuation of the right ventricular 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 involving coronary-perfused canine right ventricular (RV) wedge preparations suggest that the accentuated J wave (down-sloping ST segment elevation), which often appears as an r' resembling right bundle branch block (RBBB), in Brugada patients may be due in large part to early repolarization of right ventricular (RV) epicardium, rather than major delays in impulse conduction in the right bundle⁷⁵, although right ventricular outflow tract (RVOT) conduction delays undoubtedly contribute to the Brugada phenotype.⁷⁶ Despite the appearance of a typical Brugada sign, accentuation of the RV epicardial action potential (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 transmural dispersion of repolarization 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.^{77, 78} Support for these hypotheses derives from experiments involving the arterially perfused right ventricular wedge preparation^{77, 79–82} and from studies in which monophasic action potential (MAP) electrodes where positioned on the epicardial and endocardial surfaces of the right ventricular outflow tract (RVOT) in patients with the Brugada syndrome.^{83, 84}

Short QT Syndrome

The Short QT syndrome (SQTS) was first described as a clinical entity in 2000 by Gussak et al.⁸⁵ SQTS is an inherited syndrome characterized by a $QTc \leq 300$ msec and high incidence

of VT/VF in infants, children and young adults.⁸⁶ The familial nature of this sudden death syndrome was highlighted by Gaita et al. in 2003.⁸⁷ The first genetic defect responsible for the short QT syndrome (SQT1), 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} .⁸⁸ A second gene was recently reported by Bellocq et al. (SQT2)⁸⁹ 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.

Two additional genes recently linked to SQTs encode the $\alpha 1$ (CACNA1C) and β (CACNB2b) subunits of the L-type cardiac calcium channel. SQT4 caused by mutations in the α subunit of calcium channel have been shown to lead to QT interval <360 ms, whereas SQT5 caused by mutations in the β subunit of the calcium channel are characterized by QT intervals of 330–360 msec.⁷² Mutations in the α and β subunits of the calcium channel may also lead to ST segment elevation, creating a combined Brugada/Short QT syndrome.⁷²

In SQT1, 2 and 3, the ECG commonly displays tall peaked symmetrical T waves, due to acceleration of phase 3 repolarization. An augmented Tpeak-Tend interval associated with this electrocardiographic feature of the syndrome suggests that TDR is significantly increased (Figure 3). Evidence in support of the hypothesis derives from studies of a left ventricular wedge model of the short QT syndrome demonstrating that an increase in outward repolarizing current can preferentially abbreviate endocardial/M cell action potential, thus increasing TDR and creating the substrate for reentry.⁹⁰ 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.⁹⁰

Role of TDR in Channelopathy-induced Sudden Cardiac Death

The three inherited sudden cardiac death syndromes discussed above differ with respect to the behavior of the QT interval (Figure 4). 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. What these three syndromes have in common is an amplification of TDR, which results in the development of polymorphic ventricular tachycardia and fibrillation when dispersion of repolarization and refractoriness reaches the threshold for reentry. The threshold for reentry decreases as APD and refractoriness are reduced and the pathlength required for establishing a reentrant wave is progressively reduced.

Catecholaminergic Polymorphic VT

To what extent does an increase in TDR contribute to arrhythmogenesis in other channelopathies? Catecholaminergic polymorphic ventricular tachycardia (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 (BVT), monomorphic and polymorphic VT (PVT), and a high risk of sudden cardiac death (30–50% by the age of 20 to 30 years).^{91,92} Mutations in genes encoding the cardiac ryanodine receptor 2 (RyR2) or calsequestrin 2 (CASQ2) in patients have been associated with this phenotype.^{93–96} Mutations in RyR2 cause autosomal dominant CPVT, whereas mutations in CASQ2 are responsible for either an autosomal recessive or dominant form of CPVT.

Abundant evidence points to delayed afterdepolarization (DAD)-induced triggered activity (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 use of 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. 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.

It was noted that ectopic activity or VT that arose from epicardium was 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 now induced a very rapid polymorphic VT that would be expected to lead hemodynamic compromise.⁹⁷ Thus, even in a syndrome in which arrhythmogenesis is traditionally ascribed to triggered activity, sudden cardiac death may be due to amplification of TDR, giving rise to reentrant VT/VF.

Conclusion

The available evidence suggests that amplification of spatial dispersion of refractoriness in ventricular myocardium, particularly when due to augmentation of transmural dispersion of repolarization, can predispose to the development of potentially lethal reentrant arrhythmias in a variety of ion channelopathies including long QT, short QT and Brugada syndromes as well as catecholaminergic ventricular tachycardia. Although not discussed in this review, these same principles apply to arrhythmogenesis associated with hypertrophic and dilated cardiomyopathies^{98–101} as well as some arrhythmias associated with ischemia and reperfusion.^{102, 103}

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Abbreviations

AP, action potential; APD, action potential duration; APD₉₀, APD values at 90 percent repolarization; BrS, Brugada Syndrome; BVT, bidirectional ventricular tachycardia; CASQ2, calsequestrin 2; CPVT, catecholaminergic polymorphic ventricular tachycardia; DAD, delayed afterdepolarization; EAD, early afterdepolarization; GPD1L, Glycerol-3-Phosphate Dehydrogenase 1-Like Gene; I_{K1}, inward rectifier current; I_{Na}, sodium channel current; I_{Na-Ca}, sodium-calcium exchange current; I_{Ca}, calcium channel current; I_{Kr}, rapidly activating delayed rectifier current; I_{Ks}, slowly activating delayed rectifier current; LQTS, long QT syndromes; LQT7, Andersen–Tawil syndrome; LQT8, Timothy syndrome; MAP, monophasic action potential; PVT, polymorphic VT; RBBB, right bundle branch block; RV, right ventricular; RVOT, right ventricular outflow tract; RyR2, ryanodine receptor 2; SQTs, Short QT syndrome; TA, triggered activity; TdP, Torsade de Pointes; TDR, transmural dispersion of repolarization; VF, ventricular fibrillation; VT, ventricular tachycardia..

Long QT Syndrome

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

Brugada Syndrome

Figure 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 from,¹⁰⁴ with permission.

Figure 3.

Proposed mechanism for arrhythmogenesis in the short QT syndrome. An increase in net outward current due to a reduction in late inward current or augmentation of outward repolarizing current serves to abbreviate action potential duration heterogeneously leading to an amplification of transmural dispersion of repolarization and the creation of a vulnerable window for the development of reentry. Reentry is facilitated both by the increase in TDR and abbreviation of refractoriness.

Figure 4.

The role of transmural dispersion of repolarization (TDR) in channelopathy-induced sudden cardiac 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.

Inherited Disorders Caused by Ion Channelopathies

Rhythm	Inheritance	Locus	Ion Channel	Gene
Long QT syndrome	AD	11p15 7q35 3p21 4q25 21q22 21q22 17q23 6q8A 3p25 11q23.3	I _{Ks} I _{Kr} I _{Na} I _{Ks} I _{Kr} I _{K1} I _{Ca-L} I _{Na} I _{Na}	KCNQ1, KvLQT1 KCNH2, HERG SCN5A, Na _v 1.5 ANKB, ANK2 KCNEL, minK KCNK2, MiRP1 KCNJ2, Kir 2.1 CACNA1C, Ca _v 1.2 CAV3, Caveolin-3 SCN4B, Na _v 1.4
LQT syndrome (JLN)	TdP	AR	I _{Ks} I _{Ks}	KCNQ1, KvLQT1 KCNEL, minK
Brugada syndrome	PVT PVT PVT PVT	AD AD AD AD	I _{Na} I _{Na} I _{Ca} I _{Ca}	SCN5A, Na _v 1.5 GPDIL CACNA1C, Ca _v 1.2 CACNB2b, Ca _v β _{2b}
Short QT syndrome	VT/VF	AD	I _{Kr} I _{Ks}	KCNH2, HERG KCNQ1, KvLQT1
Catecholaminergic VT	VT VT	AD AR	I _{K1} I _{Ca}	KCNJ2, Kir2.1 CACNA1C, Ca _v 1.2 CACNB2b, Ca _v β _{2b}
				RyR2 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