GORDON K. MOE LECTURE

Heterogeneity and cardiac arrhythmias: An overview

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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. In the long QT syndrome, amplification of TDR often is secondary to preferential prolongation of the action potential duration of M cells, whereas in Brugada syndrome, it is thought to be due to selective abbreviation of the action potential duration of right ventricular epicardium. In the short QT syndrome, preferential abbreviation of action potential duration of either endocardium or epicardium appears to be responsible for amplification of TDR. In catecholaminergic polymorphic ventricular tachycardia, reversal of the direction of activation of the ventricular wall is responsible for the increase in TDR. Thus, the long QT, short QT, Brugada, and catecholaminergic ventricular tachycardia syndromes are pathologies with very different phenotypes and etiologies. However, these syndromes 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

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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 review some of our work of recent years that has served to extend and build on this theme. My focus is on evidence supporting 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 Brugada syndromes as well as catecholaminergic polymorphic ventricular tachycardia (VT). In the long QT syndrome, amplification of TDR often is secondary to preferential prolongation of the action potential duration (APD) of M cells, whereas in 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, reversal of the direction of activation of the ventricular wall appears to be responsible for the increase in TDR.

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 VT known as *torsades 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 LQTS. 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]

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Table 1 Inherited 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, Kir2.1*
	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*
Long QT syndrome (Jervell and Lange-Nielsen)		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*
	BrS3	PVT	AD	12p13.3	I_{Ca}	*CACNA1C, $Ca_V1.2$*
	BrS4	PVT	AD	10p12.33	I_{Ca}	*CACNB2b, $Ca_V\beta_{2b}$*
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*
	SQT4			12p13.3	I_{Ca}	*CACNA1C, $Ca_V1.2$*
	SQT5		AD	10p12.33	I_{Ca}	*CACNB2b, $Ca_V\beta_{2b}$*
Catecholaminergic polymorphic ventricular tachycardia	CPVT1	VT	AD	1q42–43		*RyR2*
	CPVT2	VT	AR	1p13–21		*CASQ2*

AD = autosomal dominant; AR = autosomal recessive; LQT = long QT; PVT = polymorphic ventricular tachycardia; RW = Romano-Ward; TdP = torsades de pointes; VF = ventricular fibrillation; VT = ventricular tachycardia.

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 multiorgan 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, which are 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 two 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). Six 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 potential[16] 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. Amplification of spatial dispersion of refractoriness can take the form of an increase of transmural, transseptal, or apicobasal dispersion of repolarization. This exaggerated intrinsic heterogeneity together with early afterdepolarization (EAD)–and delayed afterdepolarization (DAD)–induced triggered activity, both caused by reduction in net repolarizing current, underlie the substrate and trigger for development of TdP arrhythmias observed under LQTS conditions (Figure 1).[23,24] Models of the LQT1, LQT2, and LQT3 forms of LQTS 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 TDR,