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Mechanisms underlying arrhythmogenesis in long QT syndrome☆

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Abstract Long QT syndrome is a disease of delayed ventricular repolarization. It manifests clinically as recurrent syncope and sudden cardiac death caused by an atypical form of polymorphic ventricular tachycardia known as torsades de pointes (TdP). Evidence obtained from the studies using the rabbit left and right ventricular wedge preparations indicates that the development of TdP is relying not only on the genesis of an R-on-T trigger, but also on the formation of a functional reentrant substrate. When ventricular endocardial or subendocardial repolarization is prolonged either because of gene mutations or by drugs that reduce the net repolarization current, cell membrane potential fluctuates during phase 2 of the action potential phase 2 because of reactivation of L-type calcium current, that is, the appearance of phase 2 early afterdepolarization (EAD). In the rabbit left ventricular wedge, QT prolongation and EAD due to pure I_{Kr} inhibition are accompanied by a disproportional increase in transmural dispersion of repolarization (TDR). Early afterdepolarization in endocardium or subendocardium is able to produce new action potentials in cells with a relatively short action potential duration (eg, ventricular epicardium) probably via an electrotonic effect when TDR is large enough. This, in turn, results in an R-on-T extrasystole that is capable of initiating TdP. Enhanced TDR is essential not only for the genesis of the first initiating beat of TdP by facilitating the propagation of EAD, but also for the maintenance of TdP by serving as a functional reentrant substrate.

Keywords: Long QT syndrome; Arrhythmogenesis; Torsades de pointes

1. Introduction

Long QT syndrome (LQTS) is an either inherited or acquired disorder of delayed ventricular repolarization in humans, characterized by an excessively prolonged QT interval on the body surface electrocardiogram (ECG). It often manifests clinically as recurrent syncope or sudden cardiac death because of polymorphic ventricular tachycardia known as torsades de pointes (TdP) [1-5]. Although congenital LQTS from gene mutations in cardiac ionic channels responsible for ventricular repolarization is relatively rare and occurs with an estimated prevalence of 1 in 5000 individuals, it causes recurrent syncope in more than 50% of gene carriers and 3000 to 4000 sudden deaths in children and young adults each year in the United States [6,7]. On the other hand, acquired LQTS, particularly associated with the use of various drugs, is common, generating concerns in clinical practice as well as in drug development [2,8]. In this review article, we discuss recent advances pertinent to underlying mechanisms for LQTS and its arrhythmogenesis.

2. Ionic and cellular basis for LQTS

According to biophysical principles of ECG recording, the QT interval reflects the time from beginning of

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ventricular activation to the end of ventricular repolarization [4,9]. If the ventricular myocardium were uniform in repolarization, T wave would be a narrowly based waveform with the polarity opposite to that of the QRS complex [10]. That a narrow QRS complex is associated with a broadly based and concordant T wave in most ECG leads under physiological condition indicates that ventricular repolarization sequence is different from that of ventricular activation [11]. An upright T wave is the consequence of repolarization dispersion across the ventricles [12]. Although the interest of scientists in the genesis of the T wave began more than 100 years ago when the ECG recording was in its infancy, the debate on cellular basis for the T wave had never stopped until last decade when 3 different cell types with different repolarization properties (ie, epicardium, subendocardium [M cells], and endocardium) within the ventricular wall were identified [1,11,13,14].

Epicardial, endocardial, and M cells differ primarily from each other by their repolarization properties. The hallmark of M cells is their tendency to have their action potentials prolong disproportionately to epicardium or endocardium during bradycardia or in the presence of QT prolonging drugs. Hence, M cells are thought to play an important role in delayed ventricular repolarization as in LQTS. The ionic basis for the features of M cells that distinguish them from epicardium and endocardium includes the presence of a smaller I_{Ks} but a larger late I_{Na} [1,15]. On the other hand, I_{Kr}, the ionic target by most action potential duration (APD) prolonging agents, is similar in density among 3 cell types. Thus, the difference in I_{Ks}/I_{Kr} ratio among 3 transmural cell types plays an important role in the genesis of the T wave (Fig. 1). It has been demonstrated that the mutations of genes that encode I_{Ks} and I_{Kr} account for most forms of congenital LQTS [3,16]. Any factors that alter the I_{Ks}/I_{Kr} ratio could result in abnormal ventricular repolarization that may manifest as a variety of T-wave morphologies [17-19].

As demonstrated in Fig. 1, separation of the epicardial action potentials from that of M cells during plateau phase marks the beginning of the upright T wave. Under normal condition, the separation is so gradual that the beginning of the T wave is difficult to determine. Repolarization of the M cells is temporally aligned with the end of the T wave (T_{end}), whereas repolarization of the epicardium is coincident with the peak of the T wave (T_{peak}). Therefore, the interval from T_{peak} to T_{end} ($T_{p\text{-}e}$) that encompasses the descending limb of the T wave closely represents transmural dispersion of repolarization (TDR). This is probably the reason why the descending limb of the T wave is "vulnerable," so that an electrical impulse interrupting it (the R-on-T phenomenon) could potentially produce functional transmural reentry, leading to the development of polymorphic ventricular tachycardia or TdP (see Section 3). The $T_{p\text{-}e}$ interval, as an index of

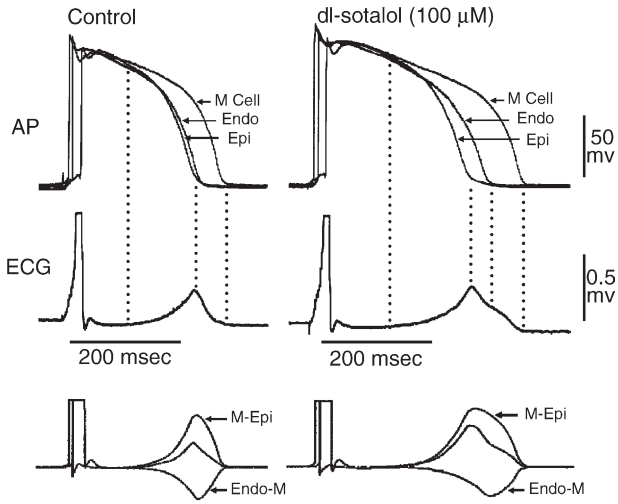

Fig. 1. Cellular basis for the QT interval. Top, Action potentials simultaneously recorded from endocardium, subendocardium, and epicardium of an isolated arterially-perfused canine left ventricular wedge preparation. A transmural ECG was recorded concurrently. Bottom, Computed voltage gradients among epicardium, subendocardium, and endocardium. Under control conditions, the T wave begins when the plateau of epicardial action potential separated from M cells. As epicardium repolarizes, the voltage gradient between the subendocardial region and epicardium continues to grow, giving rise to the ascending limb of the T wave. When epicardium is fully repolarized, the gradient reaches to a peak that marks the peak of the T wave. As the M cells continue to repolarize, the gradient between the M cells and epicardium diminishes, contributing to the descending limb of the T wave. When the M cells are fully repolarized, there is no voltage gradient that marks the end of the T wave. Because the M region is adjacent to endocardium, the gradient between 2 layers contributes less to the T wave but may play an important role in the genesis of notched T wave or pathological U wave under pathological conditions. Sotalol preferentially prolongs M cell action potential, leading to QT prolongation and a notched T wave with a prolonged descending limb. Endo indicates endocardium; M cell, subendocardium; Epi, epicardium. Reprinted with permission from Ref. [11].

TDR, has been proved to be clinically useful in assessing arrhythmic risk [20-22].

3. Mechanisms underlying arrhythmogenesis in LQTS

It is widely accepted that TdP is triggered by ventricular action potential phase 2 early afterdepolarization (EAD) under conditions of a prolonged QT interval and enhanced TDR [4,11,17,23].

As previous studies have shown, EAD-dependent R-on-T extrasystole initiates the onset of TdP under conditions of excessively delayed ventricular repolarization [4,17,18,23]. Early afterdepolarization, as the trigger, plays a central role in the development of TdP. Because the L-type calcium channel (I_{Ca}) is the primary charge carrier for EADs under delayed ventricular repolarization and its reactivation is dependent not only on time, but also on membrane potential [24,25], the following conditions facilitate occurrence of EAD: (1) delayed ventricular repolarization (ie, QT prolongation) that provides a prolonged time window for I_{Ca}