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Review

Arrhythmogenic mechano-electric heterogeneity in the long-QT syndrome

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ABSTRACT

Since the first linkage of the long-QT syndrome to the Harvey *ras*-1 gene in 1991 ample research has been performed to decipher the molecular-biophysical basis of congenital repolarization defects and the electrophysiological mechanisms of torsades-de-pointes arrhythmias in this condition. Mechanistic knowledge is mostly derived from cellular experiments (cardiac myocytes, cultured cells), ventricular tissue (including arterially-perfused wedge) preparations and Langendorff-perfused hearts, with relatively little information from in-vivo animal models, and even more scant intact human-heart investigations. Until now, much emphasis has been put on purely membrane-related pathways of arrhythmia initiation with a prominent role for spatiotemporal dispersion of repolarization, early afterdepolarizations and reentrant excitation. Here, we review additional factors that influence the onset of torsades de pointes, notably myocardial Ca^{2+} (over) loading and spontaneous SR Ca^{2+} release, occurring particularly during intense sympathetic nervous stimulation and dynamic cycle-length changes. Recent tissue and in-vivo data suggest that spontaneous SR Ca^{2+} release, underlying aftercontractions in the isolated myocyte, may organize to local myocardial Ca^{2+} waves and aftercontractions in the intact heart. In the setting of prolonged repolarization and a negative electromechanical window, these spontaneous $[Ca^{2+}]_{cyt}$-based events (which often arise during early diastole) may exaggerate repolarization instability via $[Ca^{2+}]_{cyt}$-activated inward membrane currents and, as we postulate, via mechano-sensitive ion currents. Future long-QT research should focus on the intact beating heart with preserved autonomic input to examine these arrhythmogenic mechanisms.

Contents

Abbreviations: AP, action potential; APD, action-potential duration; CaMKII, Ca^{2+}/Calmodulin-dependent serine-threonine protein kinase II; CaM, Ca^{2+}/Calmodulin complex; cAMP, cyclic adenosine monophosphatase; DAD, delayed afterdepolarization; EAD, early afterdepolarization; ERG, ether-à-go-go-related gene; EMW, electromechanical window; I_{CaL}, voltage-dependent L-type Ca^{2+} current; $I_{Cl(Ca)}$, Ca^{2+}-activated Cl^- current; I_{K1}, inward-rectifier K^+ current; $I_{K,ATP}$, adenosine triphosphate-dependent inward rectifier K^+ current; I_{Kr}, rapidly-activating delayed-rectifier K^+ current; I_{Ks}, slowly-activating delayed-rectifier K^+ current; I_{Na}, fast Na^+ current; I_{Na-Ca}, Na^+/Ca^{2+}-exchange current; I_{ti}, transient inward current; I_{to}, transient-outward K^+ current; KCNE1, potassium voltage-gated channel, subfamily E, member 1; KCNH2, potassium voltage-gated channel, subfamily H, member 2; KCNQ1, potassium voltage-gated channel,, KQT-like subfamily, member 1; LQTS, long-QT syndrome; LV, left ventricle; MAP, monophasic action potential; NCX, Na^+/Ca^{2+} exchanger isoform 1; PKA, protein kinase A; ROC, receiver operating characteristic; RV, right ventricle; RyR, ryanodine receptor; SAC_{NS}, non-selective cationic stretch-activated channel; SAC_K, K^+-selective stretch-activated channel; SCN_5A, alpha-subunit of cardiac Na^+ channel, voltage-gated, type V; SERCA, sarcoplasmic-reticulum Ca^{2+} ATPase; SR, sarcoplasmic reticulum; TDI, tissue-Doppler imaging; TdP, torsades de pointes; TRP, transient receptor potential; TRPM, melastatin transient receptor potential; VT, ventricular tachycardia.

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1. Introduction

Intrinsic electromechanical heterogeneity is present in the normal beating heart. Differences in action-potential (AP) morphology and duration exist between various regions of the ventricular myocardium under physiological conditions (Antzelevitch, 2007; Szentadrassy et al., 2005). Likewise, spatial gradients of contraction and relaxation exist, e.g., between the endo- and epicardium, apex and base, left (LV) and right ventricle (RV), and at the circumferential diameter (Brutsaert, 1987). Differential expressions of transmembrane ion currents, and Ca^{2+}-transport and storage mechanisms underlie these non-uniformities.

In patients with the congenital long-QT syndrome (LQTS), electromechanical heterogeneity of the ventricles is often increased. The various LQTS that have been identified to date are caused by genetic mutations in ion-channel subunits or ion-channel-associated proteins. Mutation carriers may remain asymptomatic during their entire life, but severe cases are susceptible to syncope or sudden death due to torsades de pointes (TdP) and ventricular fibrillation. Although these syndromes are considered "primary electrical cardiomyopathies", LQT patients may exhibit mechanical wall abnormalities under basal conditions. One initial echocardiographic study revealed a rapid early contraction and a very prolonged phase of wall thickening before rapid relaxation in more than half of referred patients, who had an averaged QTc interval of approximately 500 ms (Nador et al., 1991). In some of these, a peculiar double-peak pattern of later thickening was observed. Similar results were obtained by other groups using M-mode (Nakayama et al., 1998) and tissue-Doppler imaging techniques (Savoye et al., 2003). Mechanical wall abnormalities were normalized by intravenous treatment with the Ca^{2+}-channel blocker verapamil (De Ferrari et al., 1994). More recently, strain-imaging studies revealed that contraction duration was longer in the subendocardium than midmycardium of symptomatic LQT mutation carriers, but not of asymptomatic or healthy individuals, indicating transmural mechanical dispersion in the former group (Haugaa et al., 2010). Prolonged contraction duration and augmented longitudinal mechanical dispersion were superior to QTc for arrhythmia-risk assessment.

While these clinical data hint to an association between increased mechanical heterogeneity and the occurrence of arrhythmias in susceptible LQT patients, a mechanistic link remains elusive. This applies particularly to the dynamic beat-to-beat instabilities of the heart just prior to the onset of TdP when sympathetic activity is often enhanced. Does mechano-electric coupling contribute to arrhythmogenesis at these very instances? And if so, how?

In the present article, we review the literature on arrhythmia mechanisms in the setting of congenitally prolonged and/or dispersed ventricular repolarization, focusing mainly on the role of altered myocardial Ca^{2+} handling, spontaneous sarcoplasmic reticulum (SR) Ca^{2+} release and the generation of after-depolarizations, aftercontractions, and premature ectopic beats. The concept of the "electromechanical window" will be discussed. We will argue that in the intact beating heart, besides $[Ca^{2+}]_{cyt}$-dependent pathways, mechano-sensitive activation of ion channels can participate in torsadogenesis when electromechanical heterogeneity exaggerates and systolic and/or diastolic aftercontractions occur. As much as possible, we will seek in-vivo confirmation of cellular mechanisms.

2. Cellular Ca^{2+} overload and spontaneous SR Ca^{2+} release during prolonged repolarization

2.1. Ca^{2+} handling and Ca^{2+} accumulation in cardiac myocytes

Thorough insight into myocyte Ca^{2+} handling is essential for the understanding of arrhythmogenesis in a broad variety of cardiac diseases, including the LQTS (Volders et al., 2000). Under normal conditions, Ca^{2+}-induced Ca^{2+} release from the SR is triggered by sarcolemmal Ca^{2+} influx mainly through L-type Ca^{2+} channels (Fig. 1A) (Cannell et al., 1987; duBell and Houser, 1989). A rise in subsarcolemmal $[Ca^{2+}]$ by L-type Ca^{2+}-channel influx and/or Ca^{2+} diffusion from nearby ryanodine receptors (RyR) can activate these RyRs to release much more Ca^{2+} from the SR. Both subsarcolemmal $[Ca^{2+}]$ and intra-SR $[Ca^{2+}]$ influence RyR-channel gating properties (Sato and Bers, 2011). Multiple local Ca^{2+}-release events summate into a propagating whole-cell Ca^{2+} transient that activates the contractile apparatus via Ca^{2+} binding to the myofilament protein troponin C. Changes in the size of the Ca^{2+} transient feed back on transsarcolemmal Ca^{2+} fluxes, adjusting the SR Ca^{2+} content such that the size of the Ca^{2+} transient returns to its basal level.

It has long been recognized that Ca^{2+} can also be released from the SR without a preceding membrane depolarization. This process, referred to as spontaneous Ca^{2+} release, can occur under conditions of myocyte Ca^{2+} overload when $[Ca^{2+}]_{SR}$ is abnormally high (Fabiato, 1992; Fabiato and Fabiato, 1975; Lakatta, 1992; Venetucci et al., 2008). Protein-kinase-A (PKA)-dependent phosphorylation of L-type Ca^{2+} current (I_{CaL}), and PKA- and Ca^{2+}/Calmodulin-kinase II (CaMKII)-dependent modulation of SR Ca^{2+} uptake (via SERCA2a and phospholamban) have a large impact on SR Ca^{2+} levels and the incidence of spontaneous Ca^{2+} release (Heijman et al., 2011). The functional consequences of RyR phosphorylation (by PKA and/or CaMKII) are still debated (Kashimura et al., 2010). Several conditions promote $[Ca^{2+}]_{SR}$ accumulation and spontaneous SR Ca^{2+} release with self-propagating Ca^{2+} waves, including β-adrenergic receptor stimulation, rapid electrical stimulation, digitalis intoxication, and elevated extracellular $[Ca^{2+}]$ (Lakatta, 1992; Stern et al., 1988).

The Na^+/Ca^{2+} exchanger (NCX) is the main Ca^{2+}-extrusion protein for the beat-to-beat regulation of contraction and relaxation in cardiac myocytes. Because of a predominant stoichiometry of 3 Na^+ ions : 1 Ca^{2+} ion inward Na^+/Ca^{2+}-exchange current