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Cardiac repolarization. The long and short of it[#]

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Abstract

Heterogeneity of transmural ventricular repolarization in the heart has been linked to a variety of arrhythmic manifestations. Electrical heterogeneity in ventricular myocardium is due to ionic distinctions among the three principal cell types: Endocardial, M and Epicardial cells. A reduction in net repolarizing current generally leads to a preferential prolongation of the M cell action potential. An increase in net repolarizing current can lead to a preferential abbreviation of the action potential of right ventricular epicardium or left ventricular endocardium. These changes can result in amplification of transmural heterogeneities of repolarization and thus predispose to the development of potentially lethal reentrant arrhythmias. The long QT, short QT, Brugada and catecholaminergic VT syndromes are all examples of pathologies that have very different phenotypes and aetiologies, but share a common final pathway in causing sudden death via amplification transmural or other spatial dispersion of repolarization within the ventricular myocardium. These same mechanisms are likely to be responsible for life-threatening arrhythmias in a variety of other cardiomyopathies ranging from heart failure and hypertrophy, which may involve mechanisms very similar to those operative in long QT syndrome, to ischaemia and infarction, which may involve mechanisms more closely resembling those responsible for the Brugada syndrome.

Keywords

sudden death; electrocardiogram (ECG); long QT syndrome; Brugada syndrome; short QT syndrome; catecholaminergic VT

Electrical heterogeneities intrinsic to ventricular myocardium

Delineation of the differences in the electrophysiological characteristics and pharmacological profiles of endocardial, M and epicardial ventricular myocardial cells has advanced our understanding of the electrical heterogeneities intrinsic to the ventricular myocardium of the dog, guinea pig, rabbit, and human heart [1].

The action potentials of epicardial and M cells generally display a prominent transient outward current (I_{to})-mediated phase 1 that is absent in endocardial cells [1]. The early repolarization phase gives the epicardial action potential a notched appearance. In the canine heart, I_{to} and the action potential notch are much larger in right vs. left ventricular epicardium [2] and M [3] cells.

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 1990's, the M cells became the focus of intense investigation after their identification and characterization in the deep structures of the canine ventricle [4–6]. M cell distribution in the ventricular wall has been

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investigated in greatest detail in the canine left ventricle. M cells with the longest action potential duration are typically found in the deep subepicardium to midmyocardium in the lateral wall, deep subendocardium to midmyocardium in the anterior wall, and throughout the wall in the region of the outflow tracts. M cells have also been identified in the deep layers of papillary muscles, trabeculae, and interventricular septum [7]. Tissue slices isolated from the M region display an APD at 90 percent repolarization (APD_{90}) that is more than 100 msec longer than tissues isolated from the epicardium or endocardium at slow rates of stimulation (basic cycle lengths ≥2000 msec). In the intact ventricular wall, this disparity in APD_{90} is less pronounced due to electrotonic coupling of cells. 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 [8], which may be related to the sharp transition in cell orientation in this region as well as to reduced expression of connexin 43 [9,10], which is principally responsible for intracellular communication in the ventricular myocardium. The available data suggest that both the degree of electrotonic coupling and intrinsic action potential durations contribute importantly to the expression of electrical heterogeneity in the ventricular myocardium. The prolonged APD of M cells has been shown to be due to a smaller I_{Ks} and a larger late I_{na} [11,12] and sodium-calcium exchange current (I_{Na-Ca}) [13] compared with epicardial and endocardial cells. This results in a decrease in 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} produce much greater prolongation in M cell APD than that of epicardial or endocardial cells.

Role of electrical heterogeneity in the inscription of the J and T waves of the ECG

Differences in the time course of repolarization of the three predominant myocardial cell types have been shown to be largely responsible for the inscription of the J and T waves of the ECG. The transmural gradient resulting from the presence of an I_{to}-mediated notch in the epicardium but not the endocardium gives rise to the J wave, or Osborne wave [14]. 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 [15]. 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 transmural dispersion of repolarization [5,15]. The available data suggest that Tpeak-Tend measurements should be limited to precordial leads since these leads more accurately reflect transmural dispersion of repolarization. Recent studies have also 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 [16]. 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.

While the clinical applicability of these concepts remains to be fully validated, significant progress towards validation of the Tpeak-Tend interval as an index of transmural dispersion has been achieved. Lubinski et al. [17] demonstrated that this interval is increased in patients with congenital long QT syndrome. 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 [18–23]. Takenaka et al. recently demonstrated exercise-induced accentuation of the Tpeak-Tend interval in LQT1 patients, but not LQT2 [22]. These observations coupled with those of Schwartz et al. [24] demonstrating an association between exercise and risk for Torsade de Pointes (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 long QT syndrome was provided by Yamaguchi and co-workers [25]. 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. demonstrated that Tpeak-Tend, but not QTc, predicted sudden cardiac death in patients with hypertrophic cardiomypathy [21]. Most recently, Watanabe et al. demonstrated that prolonged Tpeak-Tend is associated with inducibility as well as spontaneous development of VT in high risk patients with organic heart disease [26].

Although additional work is clearly needed to assess the value 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 transmural dispersion of repolarization (TDR) rather than QT prolongation underlies the substrate responsible for the development of TdP [27–31].

Amplification of TDR as the basis for VT/VF

Long QT syndrome

The long QT syndrome (LQTS) is characterized by the appearance of long QT intervals in the ECG, a atypical polymorphic ventricular tachycardia known as Torsade de Pointes, and a relatively high risk for sudden cardiac death [32–34]. Congenital LQTS is subdivided into seven genotypes distinguished by mutations in at least six different ion genes and an structural anchoring protein located on chromosomes 3, 4, 7, 11, 17 and 21 [35–40]. Timothy syndrome, classified by some 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 mutations in $Ca_v1.2$, which encodes a portion of the calcium channel [41].

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 [42] 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 [43–47].

Amplification of spatial dispersion of repolarization within the ventricular myocardium is thought to generate the principal arrhythmogenic substrate in both acquired and congenital LQTS. The accentuation of spatial dispersion is typically secondary to an increase in transmural and transseptal dispersion of repolarization and the development of early after depolarization (EAD)-induced triggered activity underlie the substrate and trigger for the development of Torsade de Pointes arrhythmias observed under LQTS conditions [1,48]. 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 [49]. These models have shown 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, the latter providing the substrate for the development of spontaneous as well as stimulation-induced TdP [50–52].

The response to sympathetic activation displays a very different time-course in the case of LQT1 and LQT2, both in experimental models and in the clinic [48,53]. In LQT1, isoprenaline

(isoproterenol) produces an increase in TDR that is most prominent during the first two minutes, but which persists, although to a lesser extent, during steady-state. TdP incidence is enhanced during the initial period as well as during steady-state. In LQT2, isoprenaline produces only a transient increase in TDR that persists for less than 2 minutes. TdP incidence is, therefore, enhanced only for a brief period of time. These differences in time-course may explain the important differences in autonomic activity and other gene-specific triggers that contribute to events in patients with different LQTS genotypes [54,55] as well as the genotype-specific response to treatment with β blockers [56].

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, and a high incidence of sudden cardiac death secondary to a rapid polymorphic VT or VF [57]. 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 [58–60]. 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 right ventricular wall of the heart. 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 ref. [61] 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 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 J point elevation. 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 the endocardium, thus leading to inversion of the T wave.

The down-sloping ST segment elevation, or accentuated J wave, observed in experimental wedge models often appears as an R′, suggesting that the appearance of a right bundle branch block (RBBB) morphology 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 bundle [62]. Despite the appearance of a typical Brugada sign, accentuation of the RV epicardial AP notch alone does not give rise to an arrhythmogenic substrate. Such a 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 ventricular complex can trigger a reentrant arrhythmia. Because loss of the action potential dome in the epicardium is generally heterogeneous, epicardial dispersion of repolarization also develops. 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 complex capable of capturing the vulnerable window across the ventricular wall, thus triggering a circus movement reentry in the form of VT/VF [63,64]. Support for these hypotheses derives from experiments involving the arterially perfused right ventricular wedge preparation [63] and from recent studies in which monophasic action potential (MAP) electrodes where positioned on the epicardial and endocardial surfaces of the RVOT in patients with the Brugada syndrome [65,66].

Short QT syndrome (SQTS)

Proposed as a new clinical entity by Gussak et al. [67], the short-QT syndrome (SQTS) is an inherited syndrome characterized by a QTc ≤300 msec and high incidence of VT/VF in infants, children and young adults [68]. The familial nature of this sudden death syndrome was confirmed by Gaita et al. [69]. The first genetic defect responsible for the short QT syndrome, 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 in function in the rapidly activating delayed rectifier channel, I_{kr} [70]. A second gene was recently reported by Bellocq et al. [71]. A missense mutation in KCNQ1 (KvLQT1) caused a gain in function in I_{ks}.

The short QT syndrome 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 transmural dispersion of repolarization is increased. Recent data collected using a wedge model of the short QT syndrome has provided evidence in support of the hypothesis that an increase in outward repolarizing current can preferentially abbreviate endocardial/M cell APD in the left ventricle increasing TDK and thus create the substrate for reentry [72]. The potassium channel opener pinacidil causes 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 isoprenaline, leading to easier induction and more persistent VT/VF. The latter is likely to be due to the reduction in the wavelength of the reentrant circuit, which reduces the path length required for maintenance of reentry [72].

Catecholaminergic polymorphic VT

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is a rare, autosomal dominant inherited disorder, predominantly affecting children or adolescents with structurally normal hearts. It is characterized by bidirectional ventricular tachycardia (BVT), polymorphic VT (PVT), and a high risk of sudden cardiac death (30–50% by the age of 20 to 30 years) [73, 74]. 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 [75–78]. Several lines of evidence point to delayed afterdepolarization (DAD)-induced triggered activity (TA) as the mechanism underlying monomorphic or bidirectional VT in these patients. 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 wedge preparation [79]. 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 triggered activity arising from the epicardium, endocardium or the 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. Epicardial VT was associated with an increased Tpeak-Tend interval and transmural dispersion of repolarization due to reversal of the normal transmural activation sequence, thus creating the substrate for reentry, which permitted the induction of a more rapid polymorphic VT with programmed electrical stimulation, and propranolol or verapamil suppressed arrhythmic activity [79].

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