Role of spatial dispersion of repolarization in inherited and acquired sudden cardiac death syndromes

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It is a distinct honor and privilege to be invited to present the Wiggers lecture. My knowledge of Carl Wiggers derives in part from my discussions with Gordon K. Moe. Moe was my mentor, and Wiggers was his. Moe completed one year of postdoctoral work in the laboratory of Carl J. Wiggers at the School of Medicine at the Western Reserve University in Cleveland, OH, in 1940.

Among Wiggers’ many seminal contributions to physiology and medicine was his elucidation of the mechanisms responsible for ventricular fibrillation (VF). He described approaches to the prevention and treatment of conditions associated with VF (149). I am pleased to have the opportunity to present some of the work we have done to further his important contributions to our field.

My principal focus will be on the heterogeneity within the ventricular myocardium with respect to electrical activity: how this heterogeneity contributes to spatial dispersion of repolarization and the degree to which amplification of this spatial dispersion contributes to the development of life-threatening ventricular arrhythmias associated with inherited ion channelopathies (Table 1), such as long QT, short QT, and Brugada syndromes, as well as catecholaminergic polymorphic ventricular tachycardia (VT). Preferential prolongation of the action potential duration (APD) of M cells is responsible for the increase in TDR. In conclusion, long QT, short QT, Brugada, and catecholaminergic polymorphic VT syndromes are pathologies with very different phenotypes and etiologies, but they share a common final pathway in causing sudden cardiac death.

long QT syndrome; short QT syndrome; Brugada syndrome; polymorphic ventricular tachycardia; electrophysiology


This review examines the role of spatial electrical heterogeneity within the ventricular myocardium on the function of the heart in health and disease. The cellular basis for transmural dispersion of repolarization (TDR) is reviewed, and the hypothesis that amplification of spatial dispersion of repolarization underlies the development of life-threatening ventricular arrhythmias associated with inherited ion channelopathies is evaluated. The role of TDR in long QT, short QT, and Brugada syndromes, as well as catecholaminergic polymorphic ventricular tachycardia (VT), is critically examined. In long QT syndrome, amplification of TDR is often secondary to preferential prolongation of the action potential duration (APD) of M cells; in Brugada syndrome, however, it is thought to be due to selective abbreviation of the APD of the right ventricular epicardium. Preferential abbreviation of APD of the endocardium or epicardium appears to be responsible for the amplification of TDR in short QT syndrome. In catecholaminergic polymorphic VT, reversal of the direction of activation of the ventricular wall is responsible for transmural dispersion of repolarization (TDR). In conclusion, long QT, short QT, Brugada, and catecholaminergic polymorphic VT syndromes are pathologies with very different phenotypes and etiologies, but they share a common final pathway in causing sudden cardiac death.

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ELECTRICAL HETEROGENEITY WITHIN THE VENTRICULAR MYOCARDIUM

Studies conducted over the past two decades have provided evidence in support of the thesis that the ventricular myocardium comprises at least three electrophysiologically and functionally distinct cell types: epicardial, M, and endocardial cells (18, 20). These three principal ventricular myocardial cell types differ with respect to phase 1 and phase 3 repolarization characteristics (Fig. 1) (73). Ventricular epicardial and M, but not endocardial, cells generally display a prominent phase 1, because of a large 4-aminopyridine-sensitive transient outward current (I_{to}), giving the action potential a spike-and-dome, or notched, configuration. These regional differences in I_{to}, first
suggested on the basis of action potential data (71), have been
directly demonstrated in canine (73), feline (58), rabbit (53),
rat (41), ferret (37), and human (84, 148) ventricular myocytes.

Differences in the magnitude of the action potential notch
and corresponding differences in \( I_{to} \) have also been
described for canine ventricular M cells (137). This distinction is
thought to form the basis for why Brugada syndrome, a
channelopathy-mediated form of sudden death, is an RV dis-
ease.

Myocytes isolated from the epicardial region of the LV wall
of the rabbit show a higher density of cAMP-activated Cl\(^{-}\)
current than do endocardial myocytes (124). \( I_{to2} \), initially
ascribed to a K\(^{+}\) current, is now thought to be primarily due to
the Ca\(^{2+}\)-activated Cl\(^{-}\) current and is also thought to contrib-
tute to the action potential notch, but it is not known whether
this current differs among the three ventricular myocardi-
cell types (161). Wang and Cohen (141) reported a larger L-type
Ca\(^{2+}\) channel current \( (I_{Ca}) \) in canine endocardial than epicar-
dial ventricular myocytes, although other studies failed to
detect any difference in \( I_{Ca} \) among cells isolated from epicar-
dial, M, and endocardial regions of the canine LV wall (24,
42). Wang and Cohen also described a low-threshold, rap-
cidly activating and inactivating \( I_{Ca} \), consisting of an Ni\(^{2+}\)-
sensitive T-type \( I_{Ca} \) and a tetrodotoxin-sensitive \( I_{Ca} \), in all
endocardial myocytes that was small or absent in epicardial
myocytes (141).

Between the surface epicardial and endocardial layers are M
cells and transitional cells. The M cell, Masonic midmyocar-
dial Moe cell, discovered in the early 1990s, was named in
memory of Gordon K. Moe (18, 21, 112). The hallmark of the
M cell is the ability of its APD to exceed epicardial or
endocardial APD in response to a slowing of rate or in response
to agents that prolong APD (Fig. 2) (20, 22, 112).

Histologically, M cells are similar to epicardial and endo-
cardial cells. Electrophysiologically and pharmacologically,
they appear to be a hybrid between Purkinje and ventricular
cells (14). Similar to Purkinje fibers, M cells show a prominent
APD prolongation and develop early afterdepolarizations
(EAD) in response to rapidly activating delayed rectifier cur-
rent (\( I_{Kr} \)), blockers, whereas the epicardium and endocardium
do not. Similar to Purkinje fibers, M cells develop delayed
afterdepolarizations (DAD) more readily in response to agents
that Ca\(^{2+}\) \(^{2+}\) load or overload the cardiac cell. \( \alpha_1 \)-Adrenoceptor
stimulation prolongs the APD in Purkinje fibers but abbreviates
the APD in M cells and has little or no effect on APD in the
endocardium and epicardium (36).

Distribution of M cells within the ventricular wall has been
investigated in greatest detail in the LV of the canine heart.
Although transitional cells are found throughout the wall in the
canine LV, M cells displaying the longest action potentials [at
basic cycle length (BCL) \( \geq 2,000 \text{ ms} \)] are often localized in the
deep subendocardium to midmyocardium in the anterior wall
(158), deep subepicardium to midmyocardium in the lateral
wall (112), and throughout the wall in the region of the RV
outflow tract (18). M cells are also present in the deep cell
layers of endocardial structures, including papillary muscles,
trabeculae, and the interventricular septum (114). In contrast to
Purkinje fibers, M cells are not found in discrete bundles or

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AD, autosomal dominant; AR, autosomal recessive; JLN, Jervell and Lange-Nielsen; RW, Romano-Ward; TdP, torsade de pointes; VF, ventricular fibrillation; VT, ventricular tachycardia; PVT, polymorphic VT; \( I_{to} \), slowly activating delayed rectifier current; \( I_{to2} \), rapidly activating delayed rectifier current; \( I_{Ks} \), Na\(^{+}\) channel current; \( I_{K1} \), inward rectifier current; \( I_{Ca} \), Ca\(^{2+}\) channel current; GPDIL, glycerol-3-phosphate dehydrogenase 1-like gene; RyR2, ryanodine receptor 2 gene; CASQ2, calsequestrin 2 gene.
Fig. 1. Ionic distinctions among epicardial (Epi), M, and endocardial (Endo) cells. A: action potentials recorded from myocytes isolated from epicardial, endocardial, and M regions of canine left ventricle (LV). B: current-voltage (I-V) relationships for inward rectifier current ($I_{K1}$) in myocytes from epicardial, endocardial, and M regions. Values are means ± SD. C: transient outward current ($I_{to}$) recorded from epicardial, endocardial, and M cells. Values are means ± SD. D: average peak I-V relationship for $I_{to}$ of epicardial, endocardial, and M cells. Values are means ± SD. E: voltage-dependent activation of the slowly activating component of delayed rectifier K$^+$ current ($I_{Ks}$). Currents were elicited by voltage-pulse protocol (inset) in Na$^+$-, K$^+$-, and Ca$^{2+}$-free solution. F: voltage dependence of $I_{Ks}$ (current remaining after exposure to E-4031) and $I_{Kr}$ (E-4031-sensitive current). Values are means ± SE. *P < 0.05 vs. Epi or Endo. [From Liu et al. (72, 73) and Zygmunt et al. (163)]. G: reverse-mode Na$^+$/Ca$^{2+}$ exchange currents ($I_{Na-Ca}$) recorded in K$^+$- and Cl$^-$-free solutions at −80 mV. $I_{Na-Ca}$ was maximally activated by switch to Na$^+$-free external solution (arrow). H: midmyocardial Na$^+$/Ca$^{2+}$ exchanger density is 30% greater than endocardial density, calculated as peak outward $I_{Na-Ca}$ normalized by cell capacitance. Endocardial and epicardial densities were not significantly different. I: TTX-sensitive late Na$^+$ current ($I_{Na}$). Cells were held at −80 mV and briefly pulsed to −45 mV to inactivate fast $I_{Na}$ before step-wise voltage increases to −10 mV. J: normalized late $I_{Na}$ measured 300 ms into the test pulse plotted as a function of test pulse potential. [Modified from Zygmunt et al. (163).]
islets (114, 115), although there is evidence that they may be localized in discrete muscle layers. Cells with the characteristics of M cells have been described in canine, guinea pig, rabbit, pig, and human ventricles (19, 22, 23, 35, 49, 50, 70, 72, 73, 78, 96, 103, 106, 107, 111–115, 117, 121, 145, 147, 155, 158).

Myocytes enzymatically dissociated from the different layers of the LV wall typically display APD values that differ by >200 ms at slow rates of stimulation (BCL ≥2,000 ms). In the intact ventricular wall, this dispersion of APD is less pronounced (25–55 ms) because of electrotonic interaction among the different cell types. The transmural increase in APD from the epicardium to the endocardium is relatively gradual, except between the epicardium and subepicardium, where there is often a sharp increase in APD (Fig. 3). This has been shown to be due to an increase in tissue resistivity in this region (158), which may be related to the sharp transition of cell orientation in this region, as well as reduced expression of connexin 43 (90, 153), which is principally responsible for intracellular communication in the ventricular myocardium. Other studies have reported opposite results, showing higher expression of connexin 43 protein in the epicardium and endocardium than in the midmyocardium. Also pertinent to this issue is the demonstration by LeGrice et al. (69) that the density of collagen is heterogeneously distributed across the ventricular wall. A greater density of collagen in the deep subepicardium may also contribute to the resistive barrier in this region of the wall, limiting the degree of electrotonic interaction between myocardial layers. The degree of electrotonic coupling, together with the intrinsic differences in APD, determines the extent to which TDR is expressed in the ventricular myocardium (136).

In the dog, the ionic basis for these features of the M cell include a smaller slowly activating delayed rectifier current ($I_{Ks}$) (72), a larger late $Na^+$ current (late $I_{Na}$) (162), and a larger $Na^+/Ca^{2+}$ exchange current (163). In the canine heart, $I_{Kr}$ and the inward rectifier current ($I_{K1}$) are similar in the three transmural cell types. Transmural and apicobasal differences in the density of $I_{Kr}$ channels have been described in the ferret heart (31). $I_{Kr}$ message and channel protein are much larger in the ferret epicardium.

Interventricular differences of APD associated with differences of $K^+$ current were reported by Volders and co-workers (137): $I_{Ks}$ density was nearly twice as large in the RV than in the LV, whereas $I_{Kr}$ density was comparable in the RV and LV.
Some animal species also display prominent apicobasal electrical heterogeneity (25, 64). Surface electrograms recorded from the isolated Langendorff-perfused rabbit heart display significantly longer QT intervals in the apex than in the base, and this regional difference is augmented in the presence of methanesulfonalanilide class III antiarrhythmic drugs (64). In the intact canine heart in vivo, the effective refractory period is longer in the apex than in the base, and exposure to dofetilide enhances the gradient through a longer effective refractory period in the apex than in the base (25). In rabbit ventricular myocytes, Cheng et al. demonstrated a higher density of total K+ current in the base than in the apex; IK, density was higher in the base than in the apex, whereas IKr density was lower in the base than in the apex (134). Consistent with this observation, Brahmajothi et al. (31) reported that expression of ERG transcript (mRNA) and protein in ferret ventricles was more abundant in the apex than in the base.

In addition to electrical heterogeneities, recent studies have demonstrated heterogeneities in mechanical function across the ventricular wall. A number of studies have highlighted the regional differences in mechanical shortening and intracellular Ca2+ concentration cycling across the wall of the LV (42, 63, 67, 159). The Ca2+ transient that regulates cell shortening during excitation-contraction coupling is a dynamic process that is controlled by Ca2+ influx and release, as well as Ca2+ reuptake and extrusion. A prominent Ito-mediated phase 1 often present in epicardial and M cells contributes to the manifestation of a larger peak ICaL in (30, 97–99) and a more rapid rise of the Ca2+ transient and mechanical contraction. Endocardial cells exhibit slower contraction and relaxation kinetics than epicardial cells because of intrinsic differences in the contractile proteins between the epicardial and endocardial layers, as well as slower kinetics of the Ca2+ transient (42, 67, 140, 152). Xiong et al. (152) reported a greater Na+/Ca2+ exchange current and Na+/Ca2+ exchange mRNA and protein levels in epicardial than in midmyocardial and endocardial cells. Laurita and co-workers (67) reported significantly less sarcoplasmic reticulum Ca2+-ATPase (SERCA2a) expression in the subendocardial and midmyocardial layers than in the subepicardial layer, but they uncovered no significant difference in the transmural expression of Na+/Ca2+ exchange. These intrinsic transmural distinctions are thought to synchronize and improve contractile efficiency of the ventricular myocardium.

The ionic features that distinguish the M cell also sensitize it to a variety of pharmacological agents. Agents that block IKr or IKs or increase ICaL or late Iks generally produce a much greater prolongation of the APD of the M cell than of epicardial or endocardial cells, leading to amplification of TDR.

Amplification of transmural heterogeneities normally present in the early and late phases of the action potential can lead to the development of a variety of arrhythmias, including long QT, Brugada, and short QT syndromes, as well as catecholaminergic VT.

Significant progress has been made in defining the functional role of the various ion channels involved in these syndromes and in identifying the α-subunits that encode these channels and the accessory subunits and other regulatory proteins that modulate their expression and function. An excellent review of this area as it relates to the molecular determinants of cardiac repolarization was recently published by Nerbonne and Kass (87).

LONG QT SYNDROME

As its name implies, long QT syndrome is characterized by prolongation of the interval between the start of the QRS interval and the end of the T wave in the ECG. Long QT syndromes 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 torsade de points (TdP), and, in many, but not all, cases, a relatively high risk for sudden cardiac death (83, 100, 160). Ten genotypes of congenital long QT syndrome have been identified. 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) (44, 80, 89, 120, 142, 143).

Two recently genotyped forms of long QT syndrome are associated with multiorgan disease. Andersen-Tawil syndrome (89), also referred to as LQT7, is characterized by skeletal muscle periodic paralysis and frequent ectopy but relatively rare episodes of TdP, secondary to loss-of-function mutations in KCNJ2, which encodes Kir2.1, the channel conducting IK1. 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.1.2, the α-subunit of the Ca2+ channel (119). The most recent genes associated with long QT syndrome are CAV3, which encodes caveolin-3, and SCN4B, which encodes NavB4, an auxiliary subunit of the cardiac Na+ 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 SCN4B produce a gain of function in late INa, causing an LQT3-like phenotype (48, 135).

Long QT syndrome shows 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 K+ channel (KCNQ1 and KCNE1) and 2) a much more common autosomal dominant form, known as Romano Ward syndrome, caused by mutations in 10 different genes (Table 1). Eight of the 10 genes encode cardiac ion channels.

Acquired long QT syndrome refers to a QT prolongation caused by exposure to drugs that prolong the ventricular action potential (26) or QT prolongation secondary to cardiomyopathies, including dilated or hypertrophic cardiomyopathy, as well as to abnormal QT prolongation associated with bradycardia or electrolyte imbalance (77, 118, 127, 131, 138). The acquired form of the disease is far more prevalent than the congenital form and, in some cases, may have a genetic predisposition (95).

Accentuation of spatial dispersion of repolarization within the ventricular myocardium has been identified as the principal arrhythmogenic substrate in acquired and congenital long QT syndrome. The amplification of spatial dispersion of refractoriness can take the form of an increase of transmural, transseptal, or apicobasal dispersion of repolarization. This exag-
gerated intrinsic heterogeneity, together with EAD- and DAD-
induced triggered activity, both caused by reduction in net
repolarizing current, underlie the substrate and trigger for the
development of TdP arrhythmias observed under long QT
syndrome conditions (17, 27). Models of LQT1, LQT2, and
LQT3 have been developed using the canine arterially perfused
LV wedge preparation (Fig. 4) (109). These models suggest
that, in these three forms of long QT syndrome, preferential
prolongation of the M cell APD leads to an increase in the QT
interval, as well as an increase in TDR, which contributes to
the development of spontaneous, as well as stimulation-in-
duced, TdP (Fig. 5) (103, 106, 108, 129, 130). The spatial
dispersion of repolarization is further exaggerated by sympa-
thetic influences in LQT1 and LQT2, accounting for the great

![Fig. 4. LQT1, LQT2, and LQT3 models of long QT syndrome (LQTS). A–C: action potentials simultaneously recorded from endocardial, M, and epicardial sites of arterially perfused canine LV wedge preparations together with a transmural ECG. BCL = 2,000 ms. Transmural dispersion of repolarization (TDR) across the ventricular wall, defined as the difference in repolarization time between M and epicardial cells, is denoted below ECG traces. LQT1 model was mimicked using isoproterenol (Iso) + chromanol 293B (an \( I_{Ks} \) blocker). LQT2 was created using the \( I_{Kr} \) blocker \( d\)-sotalol + low extracellular \( K^+ \) concentration \( ([K^+]_o) \). LQT3 was mimicked using the sea anemone toxin ATX-II to augment late \( I_{Na} \). D–F: effect of isoproterenol (Iso) on LQT1, LQT2, and LQT3 models. In LQT1, isoproterenol produces a persistent prolongation of APD_{90} of the M cell and the QT interval (at 2 and 10 min), whereas APD_{90} of the epicardial cell is always abbreviated, resulting in a persistent increase in TDR (D). In LQT2, isoproterenol initially prolongs (2 min) and then abbreviates the QT interval and APD_{90} of the M cell to the control level (10 min), whereas APD_{90} of the epicardial cell is always abbreviated, resulting in a transient increase in TDR (E). In LQT3, isoproterenol produced a persistent abbreviation of the QT interval and APD_{90} of M and epicardial cells (at 2 and 10 min), resulting in a persistent decrease in TDR (F). *\( P < 0.0005 \) vs. control. †\( P < 0.0005 \); ††\( P < 0.005 \); †††\( P < 0.05 \) vs. 293B, \( d\)-sotalol (d-Sot), or ATX-II. [Modified from Shimizu and Antzelevitch (108, 104, 105).]
sensitivity of patients with these genotypes to adrenergic stimu-
lar (Figs. 4 and 5).

Differences in the time course of repolarization of the three predominant myocardial cell types have been shown to con-tribute 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 (155). 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. In the coronary-perfused wedge preparation, repolariza-
tion of the epicardial action potential coincides with the peak of the T wave (Tpeak), and repolarization of the M cells is coincident with the end of the T wave (Tend), so that the interval from the peak to the end of the T wave (Tpeak-Tend interval) provides a measure of TDR.

On the basis of these early studies, the Tpeak-Tend interval in precordial ECG leads was suggested to provide an index of TDR (18). Recent studies have also provided guidelines for the estimation of TDR in the case of more complex T waves, including negative, biphasic, and triphasic T waves (51). In such cases, the interval from the nadir of the first component of the T wave to the end of the T wave was shown to provide an ECG approximation of TDR.

Although these relationships are relatively straightforward in the coronary-perfused wedge preparation, extrapolation to the surface ECG recorded in vivo needs to be approached with great caution and will require careful validation. The Tpeak-Tend interval is unlikely to provide an absolute measure of transmu-
ral dispersion in vivo, as elegantly demonstrated by Xia and co-workers (151). However, changes in this parameter are thought to be capable of reflecting changes in spatial dispersion of repolarization, particularly TDR, and, thus, may be prog-
nostic of arrhythmic risk under a variety of conditions (57, 102, 125, 126, 144, 150). Takenaka et al. (125) recently demonstrated exercise-induced accentuation of the Tpeak-Tend interval in LQT1, but not LQT2, patients. These observations, coupled with those of Schwartz et al. (101), demonstrating an associ-
bation between exercise and risk for TdP in LQT1, but not LQT2, patients, point to the potential value of the Tpeak-Tend interval in forecasting risk for the development of TdP. Direct evidence in support of the Tpeak-Tend interval as an index to predict TdP in patients with long QT syndrome was provided by Yamaguchi and co-workers (154), who concluded that the Tpeak-Tend interval is more valuable than corrected QT (QTc) and QT dispersion as a predictor of TdP in patients with acquired long QT syndrome. Shimizu et al. (102) demonstrated that the Tpeak-Tend interval, but not QTc, predicted sudden cardiac death in patients with hypertrophic cardiomyopathy. In a case-controlled study comparing 30 cases of acquired brady-
arrhythmias complicated by TdP and 113 cases with uncom-
plicated bradyarrhythmias, Topilski et al. (128) found that QT, QTc, and Tpeak-Tend intervals were strong predictors of TdP, with the best single discriminator being a prolonged Tpeak-Tend interval. Watanabe et al. (144) demonstrated that a prolonged Tpeak-Tend interval is associated with inducibility, as well as spontaneous development, of VT in high-risk patients with organic heart disease.

An association between increased Tpeak-Tend interval and arrhythmic risk is therefore slowly coming into focus, but a direct validation of the Tpeak-Tend interval measured at the body surface as an index of TDR is still lacking. Guidelines for such validation have been suggested (5, 51, 155). Because the precordial leads view the electrical field across the ventricular wall, the Tpeak-Tend interval would be expected to be most representative of TDR in these leads. The precordial leads are unipolar leads placed on the chest that are referenced to the Wilson central terminal. The direction of these leads is radially toward the “center” of the heart, the center of the Einthoven triangle. In contrast to the precordial leads, the bipolar limb leads, including leads I, II, and III, do not look across the ventricular wall. Although Tpeak-Tend intervals measured in these limb leads may provide an index of TDR, they are more likely to reflect global dispersion, including apicobasal and interventricular dispersion of repolarization (88, 151).

A prominent increase in TDR is likely to be arrhythmogenic, because the dispersion of repolarization and refractoriness occurs over a very short distance (the width of the ventricular wall), creating a steep repolarization gradient (1, 4). It is the steepness of the repolarization gradient, rather than the total magnitude of dispersion, that determines its arrhythmogenic potential. Apicobasal or interventricular dispersion of repolar-
ization is less informative, because it may or may not be associated with a steep repolarization gradient and, thus, may or may not be associated with arrhythmic risk.

Another critical factor to consider is that TDR can be highly variable in different regions of the ventricular myocardium, particularly under pathophysiological conditions. Consequently, it is important to measure the Tpeak-Tend interval independently in each of the precordial leads, and it is inadvisable to average the Tpeak-Tend interval among several leads (151). Because long QT syndrome is principally an LV disorder, TDR is likely to be greatest in the LV wall or septum and, thus, to be best reflected in left precordial leads or lead V5, respectively. Yamaguchi et al. (154), in their study of acquired long QT syndrome, targeted lead V5. In contrast, because Brugada syndrome is an RV disorder, TDR is greatest in the RV free wall and, thus, is best reflected in the right precordial leads. For this reason, Castro et al. (38) targeted lead V2 in their study. The criteria for validation of the Tpeak-Tend interval as an index of TDR require that 1) individual precordial leads, and
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not bipolar limb leads, be evaluated and 2) TDR be present at baseline and significantly augmented as a result of an intervention.

Recently, Opthof and co-workers (88) set out to test the hypothesis that the Tpeak-Tend interval reflects transmural dispersion. Plunge electrodes were used to quantitate TDR and global dispersion of repolarization, and the Tpeak-Tend interval (Tp-e) was, regrettably, measured using only a single-limb lead, lead II. The use of two anesthetics, propofol and isoflurane, which are known to suppress Na+ channel currents in a variety of cells, including M cells, together with a pacing rate of 130 beats/min, resulted in little to no TDR (2.7–14.5 ms). The recording of precordial ECGs was not possible in this open-chest dog model. Thus the two fundamental criteria for validation were not met, leading the authors to conclude that “Tp-e does not correlate with TDR, but is an index of total dispersion of repolarization.” Thus the quest for direct validation or invalidation of the Tpeak-Tend interval measured at the body surface as an index of TDR continues.

Although most studies concur that the Tpeak-Tend interval provides a measure of spatial dispersion of repolarization, the extent to which an augmented Tpeak-Tend interval is prognostic for arrhythmic risk will depend on the repolarization gradient (i.e., proximity of the regions displaying disparate repolarization times). It would be helpful to know the extent to which the Tpeak-Tend interval provides an index of TDR, in which case the differences in refractoriness are certain to be within close proximity. An ideal model in which to test the hypothesis might be the chronic atrioventricular (AV)-block dog treated with I_{Ks} blockers, since changes in the Tpeak-Tend interval could be accurately correlated with TDR in a model that displays prominent TDR and, additionally, correlated with the risk for development of TdP.

The extent to which TDR exists in the normal heart in vivo has been a matter of considerable debate (18, 21, 43). The controversy derives in large part from the fact that quantitation of TDR in animals in vivo is hampered by 1) the inability to record local repolarization accurately and 2) the unavoidable use of anesthesia, which reduces TDR. These same constraints apply to the measurement of TDR in the human heart (8, 123). Indirect evidence for the presence of a prominent TDR in the human heart in the absence of general anesthesia was provided in a recent study (56). Theoretical studies have been helpful in understanding the role of electrical coupling in the expression of TDR under in vivo conditions (136).

The available data support the hypothesis that TDR, rather than QT prolongation, underlies the principal substrate for the development of TdP (9, 11, 27, 46, 54). Our working hypothesis for the development of long QT syndrome-related TdP presumes the presence of electrical heterogeneity in the form of TDR under baseline conditions and the amplification of TDR by agents that reduce net repolarizing current via a reduction in I_{Ks} or I_{Kr} or augmentation of I_{CaL} or late I_{Na} (Fig. 5). Conditions leading to a reduction of I_{Ks} or augmentation of late I_{Na} produce a preferential prolongation of the M cell action potential. As a consequence, the QT interval is prolonged and is accompanied by a dramatic increase in TDR, 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 provides 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 (70, 108).

Although agents that block I_{Kr} or 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 atrial and ventricular arrhythmias, is rarely associated with TdP. Chronic administration of amiodarone prolongs the APD in the epicardium and endocardium but increases APD less, or even decreases it at slow rates, in the M region, thereby reducing TDR (116). In a dog model of chronic complete AV block and acquired long QT syndrome, 6 wk of treatment with amiodarone produced a major QT prolongation without TdP. In contrast, after 6 wk of treatment with droneradone, TdP occurred in four of eight dogs, with the highest spatial dispersion of repolarization (105 ± 20 ms) (132).

Pentobarbital sodium 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 (111). 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 the 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 inward and outward currents. In the canine LV 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 the QT interval is further prolonged (46). 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 the QT interval without augmenting TDR. Chromanol 293B prolongs the APD of the three cell types homogeneously, neither increasing TDR nor widening the T wave. TdP is never observed under these conditions. The addition of β-adrenergic agonist, however, abbreviates the APD of epicardial and endocardial cells, but not the M cell, resulting in a marked accentuation of TDR and the development of TdP (108).

BRUGADA SYNDROME

Brugada syndrome is another inherited channelopathy in which amplification of TDR leads to the development of polymorphic VT and sudden cardiac death (10). Brugada syndrome is characterized by an elevated ST segment or J wave in the right precordial leads (V1–V3), often followed by a negative T wave. First described in 1992, Brugada syndrome is associated with a high incidence of sudden cardiac death secondary to a rapid polymorphic VT or VF (32). The ECG characteristics of Brugada syndrome are dynamic and often concealed but can be unmasked by potent Na+ channel blockers such as ajmaline, flecainide,procainamide, disopyramide, propafenone, and pilsicainide (33, 92, 110).

In >15% of Brugada syndrome probands, the syndrome is associated with mutations in SCN5A, the gene that encodes the
Over 100 mutations in SCN5A have been linked to Brugada syndrome in recent years (see Ref. 12 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 to 1) failure of Na\(^+\) channel expression, 2) a shift in the voltage and time dependence of \(I_{Na}\) activation, inactivation, or reactivation, 3) entry of the Na\(^+\) channel into an intermediate state of inactivation from which it recovers more slowly, or 4) accelerated inactivation of the Na\(^+\) channel. Negative SCN5A results generally do not rule out causal gene mutations, since the promoter region, cryptic splicing mutations, or the presence of gross rearrangements is generally not part of routine investigation. Recently, Hong et al. (62) were the first to report a variant consisting of six polymorphisms in near-complete linkage disequilibrium that occurred at an allele frequency of 22% in Asian subjects and was absent in whites and blacks.

Weiss et al. (146) described a second locus on chromosome 3, close to but distinct from SCN5A, linked to the syndrome 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 in a preliminary report as the glycerol-3-phosphate dehydrogenase 1-like (GPD1L) gene, and the mutation in GPD1L was shown to result in a reduction of \(I_{Na}\) (75).

The third and fourth genes associated with Brugada syndrome were recently identified and shown to encode the \(\alpha_1\) subunit (CACNA1C) and \(\beta\)-subunit (CACNB2b) of the L-type cardiac Ca\(^{2+}\) channel. Mutations in the \(\alpha\)- and \(\beta\)-subunits of the Ca\(^{2+}\) 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 (16).

The development of extrasystolic activity and polymorphic VT in Brugada syndrome has been shown to be due 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 RV wall of the heart (Fig. 6). Rebalancing of the currents active at the end of phase 1 can lead to accentuation of the action potential notch in the RV epicardium, which is responsible for the augmented J wave and the elevated ST segment associated with Brugada syndrome (see Refs. 7 and 10 for references). Under physiological conditions, the ST segment is isoelectric because of the absence of major transmural voltage gradients at the level of the action potential plateau. Accentuation of the RV action potential notch under pathophysiological conditions leads to exaggeration of transmural voltage gradients and, thus, accentuation of the J wave or elevation of the J point (Fig. 6). If the action potential of the epicardium continues to repolarize before that of the 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 action potential of the epicardium, causing it to repolarize after that of the endocardium, thus leading to inversion of the T wave (55, 156).

Despite an ECG that is typical for Brugada syndrome, accentuation of the RV epicardial action potential 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 TDR 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 the epicardium is generally heterogeneous, epicardial dispersion of repolarization develops as well. Conduction of the action potential dome from sites where it is maintained to regions where it has been lost, giving rise to a closely coupled extrasystole. E: extrastimulus (SI–S2 = 250 ms) applied to epicardium triggers a polymorphic ventricular tachycardia (VT). F: phase 2 reentrant extrasystole triggers a brief episode of polymorphic VT. [Modified from Fish and Antzelevitch (55).]
these hypotheses derives from experiments involving the arterially perfused RV wedge preparation (1, 55, 81, 82, 156) and from studies in which monophasic action potential electrodes were positioned on the epicardial and endocardial surfaces of the RV outflow tract in patients with Brugada syndrome (13, 65). Theoretical simulation models have provided further support and understanding of these mechanisms (40, 79).

**SHORT QT SYNDROME**

Short QT syndrome is a recently identified inherited channelopathy (61); it is characterized by a ≤360-ms QTc and high incidence of VT/VF in infants, children, and young adults (60). The familial nature of this sudden death syndrome was highlighted in 2003 by Gaita et al. (59). The first genetic defect found to be responsible for the short QT syndrome (SQTS1) involved two different missense mutations (substitution of 1 amino acid for another), resulting in the same amino acid substitution in HERG (N588K), which caused a gain of function in the \( I_{Kr} \) channel (34). A second gene (SQTS2) was reported by Bellocq et al. (28): a missense mutation in KCNQ1 (KvLQT1) caused a gain of function in \( I_{Ks} \). A third gene (SQTS3) involves KCNJ2, which encodes the inward rectifier channel. Mutations in KCNJ2 caused a gain of function in \( I_{K1} \), leading to an abbreviation of the QT interval. SQTS is associated with a QTc interval of <330 ms, which is quite as short as those of SQT1 and SQT2. Two additional genes recently linked to short QT syndrome encode the \( \alpha_1 \)-subunit (CACNA1C) and \( \beta \)-subunit (CACNB2b) of the L-type cardiac Ca\(^{2+} \) channel. SQT4 caused by mutations in the \( \alpha \)-subunit of the Ca\(^{2+} \) channel have been shown to lead to a <360-ms QT interval, whereas SQT5 caused by mutations in the \( \beta \)-subunit of the Ca\(^{2+} \) channel are characterized by 330- to 360-ms QT intervals (16). Mutations in the \( \alpha \)- and \( \beta \)-subunits of the Ca\(^{2+} \) channel may also lead to ST segment elevation, creating a combined Brugada-short QT syndrome (16).

The ECG commonly displays tall peaked symmetrical T waves in SQT1, SQT2, and SQT3 because of acceleration of phase 3 repolarization. An augmented \( T_{peak}-T_{end} \) interval associated with this ECG feature of the syndrome suggests that TDR is significantly increased (Fig. 8). Evidence in support of the hypothesis derives from studies of an LV 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 (52). The \( K^+ \) 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 persis-

![Fig. 7. Proposed mechanism for Brugada syndrome. A shift in balance of currents serves to amplify existing heterogeneities by causing loss of the action potential (AP) dome at some epicardial, but not endocardial, sites. A vulnerable window develops as a result of the dispersion of repolarization and refractoriness within the epicardium, as well as across the wall. Epicardial dispersion leads to development of phase 2 reentry, which provides the extrasystole that captures the vulnerable window and initiates VT/ventricular fibrillation (VF) via a circus movement reentry mechanism. (Modified from Antzelevitch (6).)](image)

![Fig. 8. Proposed mechanism for arrhythmogenesis in 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 APD heterogeneously, leading to amplification of TDR and creation of a vulnerable window for the development of reentry. Reentry is facilitated by increase in TDR and abbreviation of refractoriness.](image)

![Fig. 9. Role of TDR in channelopathies-induced sudden cardiac death. In long QT syndrome, QT interval increases as a function of disease or drug concentration; in Brugada syndrome, it remains largely unchanged; and in short QT syndrome, it decreases as a function of disease or drug. Long QT, short QT, and Brugada syndromes have in common the ability to amplify TDR, which results in development of torsades des pointes (TdP) when dispersion reaches threshold for reentry. Threshold for reentry decreases as APD and refractoriness are reduced. (Modified from Antzelevitch and Oliva (15).)](image)
tendent VT/VF. An increase of TDR to >55 ms was associated with inducibility of VT/VF. In long QT syndrome models, a >90-ms TDR is required to induce TdP. The easier inducibility in short QT syndrome is due to the reduction in the wavelength (refractory period × conduction velocity) of the reentrant circuit, which reduces the pathlength required for maintenance of reentry (52).

TDR AS THE COMMON DENOMINATOR IN CHANNELOPATHY-INDUCED SUDDEN CARDIAC DEATH

The three inherited sudden cardiac death syndromes discussed in this review differ with respect to the characteristics of the QT interval (Fig. 9). In the long QT syndrome, the QT interval increases as a function of disease or drug concentration; in Brugada syndrome, it remains largely unchanged; and in short QT syndrome, it decreases as a function of disease or drug. These three syndromes have in common an amplification of TDR, which results in the development of polymorphic VT and VF when dispersion of repolarization and refractoriness reaches the threshold for reentry. When polymorphic VT occurs in the setting of long QT syndrome, we refer to it as TdP. 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 VENTRICULAR TACHYCARDIA

Can arrhythmogenesis generally attributed to triggered activity be aggravated by amplification of TDR? CPVT is a rare, autosomal dominant or recessive inherited disorder that predominantly affects children or adolescents with structurally normal hearts. It is characterized by bidirectional VT, monomorphic and polymorphic VT, and a high risk of sudden cardiac death (30–50% by 20–30 yr of age) (68, 122). Mutations in genes encoding the cardiac ryanodine receptor 2 (RyR2) or calsequestrin 2 (CASQ2) in patients have been associated with this phenotype (66, 91, 93, 94). Mutations in RyR2 cause autosomal dominant CPVT, whereas mutations in CASQ2 are responsible for an autosomal recessive or dominant form of CPVT.

Numerous studies have provided evidence that DAD-induced triggered activity underlies monomorphic or bidirectional VT in patients with CPVT (74, 85). 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 Ca\(^{2+}\) homeostasis encountered under conditions that predispose to CPVT (86).

The combination of isoproterenol and caffeine was found to lead to the development of DAD-induced triggered activity arising from the epicardium, endocardium, or M region. Alternation of epicardial and endocardial sources 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. Ectopic activity or VT in the model arose from the epicardium and was associated with an increased Tpeak-Tend interval and augmented TDR due to reversal of the normal transmural activation sequence. The increase in TDR created a vulnerable window across the ventricular wall that, when invaded by a premature extrasystole, permitted the precipitation of a very rapid polymorphic VT, which would be expected to lead to hemodynamic compromise (86). 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

Amplification of spatial dispersion of refractoriness in ventricular myocardium, particularly that due to augmentation of TDR, 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 CPVT. These same principles apply to arrhythmogenesis associated with hypertrophic and dilated cardiomyopathies (2, 3, 133, 139), as well as some arrhythmias associated with ischemia and reperfusion (45, 157).

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