Published in final edited form as:

Ann N Y Acad Sci. 2005 June ; 1047: 314–323.

Modulation of Transmural Repolarization

CHARLES ANTZELEVITCH

Masonic Medical Research Laboratory, Utica, New York 13501, USA

Abstract

Ventricular myocardium in larger mammals has been shown to be comprised of three distinct cell types: epicardial, M, and endocardial. Epicardial and M cell action potentials differ from endocardial cells with respect to the morphology of phase 1. These cells possess a prominent I_{to} -mediated notch responsible for the “spike and dome” morphology of the epicardial and M cell response. M cells are distinguished from the other cell types in that they display a smaller I_{Ks} , but a larger late I_{Na} and I_{Na-Ca} . These ionic distinctions underlie the longer action potential duration (APD) and steeper APD-rate relationship of the M cell. Difference in the time course of repolarization of phase 1 and phase 3 are responsible for the inscription of the electrocardiographic J wave and T wave, respectively. These repolarization gradients are sensitively modulated by electrotonic communication among the three cell types, $[K^+]_o$, and the presence of drugs that either reduce or augment net repolarizing current. A reduction in net repolarizing current generally leads to a preferential prolongation of the M cell action potential, responsible for a prolongation of the QT interval and an increase in transmural dispersion of repolarization (TDR), which underlies the development of torsade de pointes arrhythmias. An increase in net repolarizing current can lead to a preferential abbreviation of the action potential of epicardium in the right ventricle (RV), and endocardium in the left ventricle (LV). These actions also lead to a TDR that manifests as the Brugada syndrome in RV and the short QT syndrome in LV.

Keywords

Brugada syndrome; cardiac heterogeneity; electrocardiogram; long QT syndrome; M cell; short QT syndrome

INTRODUCTION

Intrinsic Electrical Heterogeneities in Ventricular Myocardium

Our understanding of the electrophysiology and pharmacology of the ventricular myocardium has advanced in recent years with the delineation of three distinct myocardial cell types: epicardial, M, and endocardial. Differences in the electrophysiologic characteristics and pharmacologic profiles of these three myocardial cell types have been described in the dog, guinea pig, rabbit, and human ventricles.¹

The three cell types differ with respect to currents that contribute to the early re-polarization phase, phase 1. The action potentials of epicardial and M cells display a prominent transient outward current (I_{to})-mediated phase 1 that is absent in endocardial cells (see Ref. 1 for references). 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 versus left ventricular epicardium² and M³ cells.

The principal feature 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 1990s, 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 investigated in greatest detail in the canine left ventricle. M cells with the longest action potential duration (APD) 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 are also present in the deep layers of papillary muscles, trabeculae, and interventricular septum.⁷ Tissue slices isolated from the M region display an APD at 90% repolarization (APD₉₀) that is more than 100 ms longer than tissues isolated from the epicardium or endocardium at basic cycle lengths of 2000 ms or greater. In the intact ventricular wall, this disparity in APD₉₀ 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. Thus, both the degree of electrotonic coupling and intrinsic action potential durations play a key role in the expression of electrical heterogeneity in the ventricular myocardium.

The prolonged APD of M cells has been shown to be due to a number of ionic distinctions, including a smaller I_{Ks} and a larger late I_{Na} ^{11,12} and sodium-calcium exchange current (I_{Na-Ca})¹³ compared to epicardial and endocardial cells. The net result is 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 on the APD of epicardial or endocardial cells.

Electrical Heterogeneity Contributes to Inscription of J Wave and T Wave of ECG

Transmural 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 wave and T wave of the ECG. The transmural gradient resulting from the presence of an I_{to} -mediated notch in epicardium but not 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 When the T wave is upright, 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. It follows that the duration of the M cell action potential determines the QT interval, whereas the duration of the epicardial action potential determines the QT_{peak} interval. Another interesting finding stemming from these studies is that the T_{peak}-T_{end} interval may provide an index of transmural dispersion of repolarization (TDR).^{5,15}

The available data suggest that T_{peak}-T_{end} measurements should be limited to precordial leads since these leads may more accurately reflect TDR. Recent studies have also provide guidelines for the estimation of TDR 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 TDR.

The clinical applicability of these concepts remains to be fully validated. An important step toward validation of the $T_{\text{peak}}-T_{\text{end}}$ interval as an index of transmural dispersion was provided in a report by Lubinski *et al.*,¹⁷ which showed an increase of this interval in patients with congenital long QT syndrome (LQTS). Recent studies suggest that the $T_{\text{peak}}-T_{\text{end}}$ 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.*²² recently demonstrated exercise-induced accentuation of the $T_{\text{peak}}-T_{\text{end}}$ interval in LQT1 patients, but not LQT2. These observation 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, again point to the potential value of $T_{\text{peak}}-T_{\text{end}}$ in forecasting risk for the development of TdP.

Direct evidence in support of $T_{\text{peak}}-T_{\text{end}}$ as a valuable index to predict TdP in patients with LQTS was provided by Yamaguchi and co-workers.²⁵ These authors concluded that $T_{\text{peak}}-T_{\text{end}}$ is more valuable than QTc and QT dispersion as a predictor of TdP in a patient with acquired LQTS. Shimizu *et al.* demonstrated that $T_{\text{peak}}-T_{\text{end}}$, but not QTc, predicted sudden cardiac death in patients with hypertrophic cardiomyopathy.²¹ Most recently, Watanabe *et al.* demonstrated that prolonged $T_{\text{peak}}-T_{\text{end}}$ is associated with inducibility as well as spontaneous development of ventricular tachycardia (VT) in high-risk patients with organic heart disease.²⁶ Although additional work is needed to assess the value of these noninvasive indices of electrical heterogeneity and their prognostic value in the assignment of arrhythmic risk, evidence is mounting in support of the hypothesis that TDR rather QT prolongation underlies the substrate responsible for the development of TdP.²⁷⁻³¹

AMPLIFICATION OF TRANSMURAL HETEROGENEITY AS THE BASIS FOR VT/VF

Brugada Syndrome

The Brugada syndrome is characterized by (1) an accentuated ST segment elevation or J wave appearing principally in the right precordial leads (V1-V3), often followed by a negative T wave; (2) very closely coupled extrasystoles; and (3) rapid polymorphic VT (PVT), which at times may be indistinguishable from ventricular fibrillation (VF).³² 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.³³⁻³⁵

The arrhythmogenic substrate responsible for the development of extrasystoles and PVT in the Brugada syndrome is believed 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. 36 for references). The presence of a transient outward current (I_{to})-mediated spike and dome morphology, or notch, in ventricular epicardium, but not endocardium, creates a transmural voltage gradient responsible for the inscription of the electrocardiographic J wave.^{14,37} The ST segment is normally isoelectric due to the absence of transmural voltage gradients at the level of the action potential plateau. Accentuation of the right ventricular action potential notch under pathophysiologic 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 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 morphology in Brugada patients may be due in large part to early repolarization of right ventricular epicardium, rather than major delays in impulse conduction in the right bundle.³⁸ Despite the appearance of a typical Brugada sign, accentuation of the right ventricular 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. As a consequence, a marked TDR develops, creating a vulnerable window that, when captured by a premature extrasystole, can trigger a reentrant arrhythmia. Because loss of the action potential dome in epicardium is generally heterogeneous, epicardial dispersion of repolarization develops as well. Conduction of the action potential dome from sites where it is maintained to sites where it is lost causes local reexcitation via phase 2 reentry, leading to the development of a closely-coupled extrasystole capable of capturing the vulnerable window across the ventricular wall, thus triggering a circus movement reentry in the form of VT/VF.^{39,40} Support for these hypotheses derives from experiments involving the arterially perfused right ventricular wedge preparation³⁹ and from recent studies in which monophasic action potential electrodes were positioned on the epicardial and endocardial surfaces of the right ventricular outflow tract in patients with the Brugada syndrome.^{41,42}

Long QT Syndrome

The long QT syndrome (LQTS) is characterized by the appearance of long QT intervals in the ECG, an atypical PVT known as TdP, and a high risk for sudden cardiac death.⁴³⁻⁴⁵ Congenital LQTS is subdivided into seven genotypes distinguished by mutations in at least six different ion genes and a structural anchoring protein located on chromosomes 3, 4, 7, 11, 17, and 21.⁴⁶⁻⁵¹ 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,⁵² or QT prolongation secondary to bradycardia or an electrolyte imbalance. In recent years this syndrome has been extended to encompass the reduced repolarization reserve attending remodeling of the ventricular myocardium that accompanies dilated and hypertrophic cardiomyopathies.⁵³⁻⁵⁷

Amplification of spatial dispersion of repolarization within the ventricular myocardium is thought to generate the principal arrhythmogenic substrate. The accentuation of spatial dispersion is typically secondary to an increase of transmural and transseptal dispersion of repolarization and the development of early afterdepolarization-induced triggered activity (TA) underlie the substrate and trigger for the development of TdP arrhythmias observed under LQTS conditions.^{1,58} Models of the LQT1, LQT2, and LQT3 forms of the LQTS syndrome have been developed using the canine arterially perfused left ventricular wedge preparation.⁵⁹ 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.⁶⁰⁻⁶²

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.^{58,63} In LQT1, isoproterenol produces an increase in TDR that is most prominent during the first 2 min, but which persists, to a lesser extent, during steady-state. TdP incidence is enhanced during the initial period as well as during steady-state. In LQT2, isoproterenol produces only a transient increase in TDR that persists for less than 2 min. 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.^{64,65}

Short QT Syndrome

The short QT syndrome (SQTs) was proposed as a new clinical entity by Gussak *et al.* in 2000.⁶⁶ SQTs is an inherited syndrome characterized by a QTc $\leq$ 300 ms and high incidence of VT/VF in infants, children, and young adults.⁶⁷ The familial nature of this sudden death syndrome was confirmed by Gaita *et al.* in 2003.⁶⁸ The first genetic defect responsible for the short QT syndrome, reported by Brugada *et al.* in 2004, involved two different missense mutations resulting in the same amino acid substitution in HERG (N588K), which caused a gain of function in the rapidly activating delayed rectifier channel, I_{Kr} .⁶⁹ A second gene was recently reported by Bellocq *et al.*⁷⁰ A missense mutation in KCNQ1 (KvLQT1) caused a gain of function in I_{Ks} .

A distinctive electrocardiographic feature of the short QT syndrome is the appearance of tall peaked symmetrical T waves. The augmented $T_{peak}-T_{end}$ interval associated with this electrocardiographic feature of the syndrome suggests that TDR is increased. Recent preliminary data from a wedge model of the short QT syndrome has provided evidence in support of the hypothesis that an increase in outward repolarizing current can increase TDR and thus create the substrate for reentry. 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. PVT could be readily induced with programmed electrical stimulation. The increase in TDR was further accentuated by isoproterenol, leading to easier induction and more persistent VT/VF. The latter is likely due to the reduction in the wavelength of the reentrant circuit, which reduces the pathlength required for maintenance of reentry.⁷¹

Catecholaminergic Polymorphic VT

Catecholaminergic, or familial, 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), PVT, and a high risk of sudden cardiac death (30% to 50% by the age of 20 to 30 years).^{72,73} Recent molecular genetic studies have identified mutations in genes encoding for the cardiac ryanodine receptor 2 or calsequestrin 2 in patients with this phenotype.⁷⁴⁻⁷⁷ Several lines of evidence point to delayed after-depolarization (DAD)-induced TA as the mechanism underlying monomorphic VT (MVT) or BVT in these patients. The cellular mechanisms underlying the various ECG phenotypes, and the transition of MVT to PVT or VF, were recently elucidated with the help of the wedge preparation.⁷⁸ The wedge was exposed to low-dose caffeine to mimic the defective calcium homeostasis encountered under conditions that predispose to CPVT. The combination of isoproterenol and caffeine led to the development of DAD-induced TA arising from epicardium, endocardium, or the M region. Migration of the source of ectopic activity was responsible for the transition from MVT to slow PVT. Alternation of epicardial and endocardial source of ectopic activity gave rise to a BVT. Epicardial VT was associated with an increased $T_{peak}-T_{end}$ interval and TDR due to reversal of the normal transmural activation sequence, thus creating the substrate for reentry, which permitted the induction of a more rapid PVT with programmed electrical stimulation. Propranolol or verapamil suppressed arrhythmic activity.⁷⁸

CONCLUSION

Amplification of transmural heterogeneities of repolarization in ventricular myocardium can predispose to the development of potentially lethal reentrant arrhythmias. The long QT, short

QT, Brugada, and catecholaminergic VT syndromes are examples of pathologies that have very different phenotypes and etiologies, but share a common final pathway in causing sudden death. These same mechanisms are likely 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 LQTS, to ischemia and infarction, which may involve mechanisms more closely resembling those responsible for the Brugada syndrome.

ACKNOWLEDGMENTS

This work was supported by grants from the National Institutes of Health (HL-47678), American Heart Association-New York state affiliate, and the Masons of New York state and Florida.

REFERENCES

1. ANTZELEVITCH, C.; DUMAINE, R. Electrical heterogeneity in the heart: physiological, pharmacological and clinical implications. In: Page, E.; Fozzard, H.; Solaro, R.J., editors. Handbook of Electrophysiology: The Heart. Oxford University Press; New York: 2002. p. 654-692.
2. DI DIEGO JM, SUN ZQ, ANTZELEVITCH C. I_{to} and action potential notch are smaller in left vs. right canine ventricular epicardium. *Am J Physiol* 1996;271:H548-H561. [PubMed: 8770096]
3. VOLDERS PG, SIPIDO KR, CARMELIET E, et al. Repolarizing K⁺ currents ITO1 and IKs are larger in right than left canine ventricular midmyocardium. *Circulation* 1999;99:206-210. [PubMed: 9892584]
4. SICOURI S, ANTZELEVITCH C. A subpopulation of cells with unique electro-physiological properties in the deep subepicardium of the canine ventricle. The M cell. *Circ. Res* 1991;68:1729-1741. [PubMed: 2036721]
5. ANTZELEVITCH CW, SHIMIZU GX, YAN, et al. The M cell: its contribution to the ECG and to normal and abnormal electrical function of the heart. *J. Cardiovasc. Electrophysiol* 1999;10:1124-1152. [PubMed: 10466495]
6. ANYUKHOVSKY EP, SOSUNOV EA, GAINULLIN RZ, et al. The controversial M cell. *J. Cardiovasc. Electrophysiol* 1999;10:244-260. [PubMed: 10090229]
7. SICOURI S, FISH J, ANTZELEVITCH C. Distribution of M cells in the canine ventricle. *J. Cardiovasc. Electrophysiol* 1994;5:824-837. [PubMed: 7874328]
8. YAN GX, SHIMIZU W, ANTZELEVITCH C. Characteristics and distribution of M cells in arterially-perfused canine left ventricular wedge preparations. *Circulation* 1998;98:1921-1927. [PubMed: 9799214]
9. POELZING S, AKAR FG, BARON E, et al. Heterogeneous connexin43 expression produces electrophysiological heterogeneities across ventricular wall. *Am. J. Physiol. Heart Circ. Physiol* 2004;286:H2001-H2009. [PubMed: 14704225]
10. YAMADA KA, KANTER EM, GREEN KG, et al. Transmural distribution of connexins in rodent hearts. *J. Cardiovasc. Electrophysiol* 2004;15:710-715. [PubMed: 15175068]
11. ZYGMUNT AC, EDDLESTONE GT, THOMAS GP, et al. Larger late sodium conductance in M cells contributes to electrical heterogeneity in canine ventricle. *Am. J. Physiol* 2001;281:H689-H697.
12. LIU DW, ANTZELEVITCH C. Characteristics of the delayed rectifier current (IKr and IKs) in canine ventricular epicardial, midmyocardial, and endocardial myocytes. *Circ. Res* 1995;76:351-365. [PubMed: 7859382]
13. ZYGMUNT AC, GOODROW RJ, ANTZELEVITCH C. INa-Ca contributes to electrical heterogeneity within the canine ventricle. *Am. J. Physiol* 2000;278:H1671-H1678.
14. YAN GX, ANTZELEVITCH C. Cellular basis for the electrocardiographic J wave. *Circulation* 1996;93:372-379. [PubMed: 8548912]
15. YAN GX, ANTZELEVITCH C. Cellular basis for the normal T wave and the electrocardiographic manifestations of the long QT syndrome. *Circulation* 1998;98:1928-1936. [PubMed: 9799215]
16. EMORI T, ANTZELEVITCH C. Cellular basis for complex T waves and arrhythmic activity following combined I(Kr) and I(Ks) block. *J. Cardiovasc. Electrophysiol* 2001;12:1369-1378. [PubMed: 11797994]

17. LUBINSKI A, LEWICKA-NOWAK E, KEMPA M, et al. New insight into repolarization abnormalities in patients with congenital long QT syndrome: the increased transmural dispersion of repolarization. *Pacing Clin. Electrophysiol* 1998;21:172–175. [PubMed: 9474667]
18. WOLK R, STEC S, KULAKOWSKI P. Extrasystolic beats affect transmural electrical dispersion during programmed electrical stimulation. *Eur. J. Clin. Invest* 2001;31:563–569. [PubMed: 11454009]
19. TANABE Y, INAGAKI M, KURITA T, et al. Sympathetic stimulation produces a greater increase in both transmural and spatial dispersion of repolarization in LQT1 than LQT2 forms of congenital long QT syndrome. *J. Am. Coll. Cardiol* 2001;37:911–919. [PubMed: 11693770]
20. FREDERIKS J, SWENNE CA, KORS JA, et al. Within-subject electrocardiographic differences at equal heart rates: role of the autonomic nervous system. *Pflugers Arch* 2001;441:717–724. [PubMed: 11294255]
21. SHIMIZU M, INO H, OKEIE K, et al. T-peak to T-end interval may be a better predictor of high-risk patients with hypertrophic cardiomyopathy associated with a cardiac troponin I mutation than QT dispersion. *Clin. Cardiol* 2002;25:335–339. [PubMed: 12109867]
22. TAKENAKA K, AI T, SHIMIZU W, et al. Exercise stress test amplifies genotype-phenotype correlation in the LQT1 and LQT2 forms of the long-QT syndrome. *Circulation* 2003;107:838–844. [PubMed: 12591753]
23. WATANABE N, KOBAYASHI Y, TANNO K, et al. Transmural dispersion of repolarization and ventricular tachyarrhythmias. *J. Electrocardiol* 2004;37:191–200. [PubMed: 15286932]
24. SCHWARTZ PJ, PRIORI SG, SPAZZOLINI C, et al. Genotype-phenotype correlation in the long-QT syndrome: gene-specific triggers for life-threatening arrhythmias. *Circulation* 2001;103:89–95. [PubMed: 11136691]
25. YAMAGUCHI M, SHIMIZU M, Ino H, et al. T wave peak-to-end interval and QT dispersion in acquired long QT syndrome: a new index for arrhythmogenicity. *Clin. Sci. (Lond)* 2003;105:671–676. [PubMed: 12857349]
26. WATANABE N, KOBAYASHI Y, TANNO KK, et al. Transmural dispersion of repolarization and ventricular tachyarrhythmias. *J. Electrocardiol* 2004;37:191–200. [PubMed: 15286932]
27. ANTZELEVITCH C, BELARDINELLI L, ZYGMUNT AC, et al. Electrophysiologic effects of ranolazine: a novel anti-anginal agent with antiarrhythmic properties. *Circulation* 2004;110:904–910. [PubMed: 15302796]
28. DI DIEGO JM, BELARDINELLI L, ANTZELEVITCH C. Cisapride-induced transmural dispersion of repolarization and torsade de pointes in the canine left ventricular wedge preparation during epicardial stimulation. *Circulation* 2003;108:1027–1033. [PubMed: 12912819]
29. ANTZELEVITCH, C. Drug-induced channelopathies. In *Cardiac Electrophysiology: From Cell to Bedside*. In: Douglas, P.; Zipes; Jose Jalife, editors. 4th ed. W. B. Saunders; New York: 2004. p. 151-157.
30. BELARDINELLI L, ANTZELEVITCH C, VOS MA. Assessing predictors of drug-induced torsade de pointes. *Trends Pharmacol. Sci* 2003;24:619–625. [PubMed: 14654302]
31. FENICHEL RR, MALIK M, ANTZELEVITCH C, et al. Drug-induced torsade de pointes and implications for drug development. *J. Cardiovasc. Electrophysiol* 2004;15:1–21.
32. BRUGADA P, BRUGADA J. Right bundle branch block, persistent ST segment elevation and sudden cardiac death: a distinct clinical and electrocardiographic syndrome: a multicenter report. *J. Am. Coll. Cardiol* 1992;20:1391–1396. [PubMed: 1309182]
33. BRUGADA R, BRUGADA J, ANTZELEVITCH C, et al. Sodium channel blockers identify risk for sudden death in patients with ST-segment elevation and right bundle branch block but structurally normal hearts. *Circulation* 2000;101:510–515. [PubMed: 10662748]
34. SHIMIZU W, ANTZELEVITCH C, SUYAMA K, et al. Effect of sodium channel blockers on ST segment, QRS duration, and corrected QT interval in patients with Brugada syndrome. *J. Cardiovasc. Electrophysiol* 2000;11:1320–1329. [PubMed: 11196553]
35. PRIORI SG, NAPOLITANO C, GASPARINI M, et al. Clinical and genetic heterogeneity of right bundle branch block and ST-segment elevation syndrome: a prospective evaluation of 52 families. *Circulation* 2000;102:2509–2515. [PubMed: 11076825]

36. ANTZELEVITCH C. The Brugada syndrome: ionic basis and arrhythmia mechanisms. *J. Cardiovasc. Electrophysiol* 2001;12:268–272. [PubMed: 11232628]
37. FISH JM, ANTZELEVITCH C. Role of sodium and calcium channel block in unmasking the Brugada syndrome. *Heart Rhythm* 2004;1:210–217. [PubMed: 15851155]
38. GUSSAK I, ANTZELEVITCH C, BJERREGAARD P, et al. The Brugada syndrome: clinical, electrophysiologic and genetic aspects. *J. Am. Coll. Cardiol* 1999;33:5–15. [PubMed: 9935001]
39. YAN GX, ANTZELEVITCH C. Cellular basis for the Brugada syndrome and other mechanisms of arrhythmogenesis associated with ST-segment elevation. *Circulation* 1999;100:1660–1666. [PubMed: 10517739]
40. LUKAS A, ANTZELEVITCH C. Phase 2 reentry as a mechanism of initiation of circus movement reentry in canine epicardium exposed to simulated ischemia. *Cardiovasc. Res* 1996;32:593–603. [PubMed: 8881520]
41. ANTZELEVITCH C, BRUGADA P, BRUGADA J, et al. Brugada syndrome: a decade of progress. *Circ. Res* 2002;91:1114–1119. [PubMed: 12480811]
42. KURITA T, SHIMIZU W, INAGAKI M, et al. The electrophysiologic mechanism of ST-segment elevation in Brugada syndrome. *J. Am. Coll. Cardiol* 2002;40:330–334. [PubMed: 12106940]
43. SCHWARTZ PJ. The idiopathic long QT syndrome: progress and questions. *Am. Heart J* 1985;109:399–411. [PubMed: 3966369]
44. MOSS AJ, SCHWARTZ PJ, CRAMPTON RS, et al. The long QT syndrome: prospective longitudinal study of 328 families. *Circulation* 1991;84:1136–1144. [PubMed: 1884444]
45. ZIPES DP. The long QT interval syndrome. A Rosetta stone for sympathetic related ventricular tachyarrhythmias. *Circulation* 1991;84:1414–1419. [PubMed: 1760020]
46. WANG Q, SHEN J, SPLAWSKI I, et al. *SCN5A* mutations associated with an inherited cardiac arrhythmia, long QT syndrome. *Cell* 1995;80:805–811. [PubMed: 7889574]
47. MOHLER PJ, SCHOTT JJ, GRAMOLINI AO, et al. Ankyrin-B mutation causes type 4 long-QT cardiac arrhythmia and sudden cardiac death. *Nature* 2003;421:634–639. [PubMed: 12571597]
48. PLASTER NM, TAWIL R, TRISTANI-FIROUZI M, et al. Mutations in Kir2.1 cause the developmental and episodic electrical phenotypes of Andersen's syndrome. *Cell* 2001;105:511–519. [PubMed: 11371347]
49. CURRAN ME, SPLAWSKI I, TIMOTHY KW, et al. A molecular basis for cardiac arrhythmia: *HERG* mutations cause long QT syndrome. *Cell* 1995;80:795–803. [PubMed: 7889573]
50. WANG Q, CURRAN ME, SPLAWSKI I, et al. Positional cloning of a novel potassium channel gene: *KVLQT1* mutations cause cardiac arrhythmias. *Nat. Genet* 1996;12:17–23. [PubMed: 8528244]
51. SPLAWSKI I, TRISTANI-FIROUZI M, LEHMANN MH, et al. Mutations in the hminK gene cause long QT syndrome and suppress I_{Ks} function. *Nat. Genet* 1997;17:338–340. [PubMed: 9354802]
52. BEDNAR MM, HARRIGAN EP, ANZIANO RJ, et al. The QT interval. *Prog. Cardiovasc. Dis* 2001;43:1–45. [PubMed: 11269621]
53. TOMASELLI GF, MARBAN E. Electrophysiological remodeling in hypertrophy and heart failure. *Cardiovasc. Res* 1999;42:270–283. [PubMed: 10533566]
54. SIPIDO KR, VOLDERS PG, DE GROOT SH, et al. Enhanced Ca^{2+} release and Na/Ca exchange activity in hypertrophied canine ventricular myocytes: potential link between contractile adaptation and arrhythmogenesis. *Circulation* 2000;102:2137–2144. [PubMed: 11044433]
55. VOLDERS PG, SIPIDO KR, VOS MA, et al. Downregulation of delayed rectifier K^{+} currents in dogs with chronic complete atrioventricular block and acquired torsades de pointes. *Circulation* 1999;100:2455–2461. [PubMed: 10595960]
56. UNDROVINAS AI, MALTSEV VA, SABBAAHN. Repolarization abnormalities in cardiomyocytes of dogs with chronic heart failure: role of sustained inward current. *Cell. Mol. Life Sci* 1999;55:494–505. [PubMed: 10228563]
57. MALTSEV VA, SABBAAHN, HIGGINS RS, et al. Novel, ultraslow inactivating sodium current in human ventricular cardiomyocytes. *Circulation* 1998;98:2545–2552. [PubMed: 9843461]
58. ANTZELEVITCH C, SHIMIZU W. Cellular mechanisms underlying the Long QT syndrome. *Curr. Opin. Cardiol* 2002;17:43–51. [PubMed: 11790933]

59. SHIMIZU W, ANTZELEVITCH C. Effects of a K(+) channel opener to reduce transmural dispersion of repolarization and prevent torsade de pointes in LQT1, LQT2, and LQT3 models of the long-QT syndrome. *Circulation* 2000;102:706–712. [PubMed: 10931813]
60. SHIMIZU W, ANTZELEVITCH C. Cellular basis for the ECG features of the LQT1 form of the long QT syndrome: effects of b-adrenergic agonists and antagonists and sodium channel blockers on transmural dispersion of repolarization and torsade de pointes. *Circulation* 1998;98:2314–2322. [PubMed: 9826320]
61. SHIMIZU W, ANTZELEVITCH C. Sodium channel block with mexiletine is effective in reducing dispersion of repolarization and preventing torsade de pointes in LQT2 and LQT3 models of the long-QT syndrome. *Circulation* 1997;96:2038–2047. [PubMed: 9323097]
62. SHIMIZU W, ANTZELEVITCH C. Differential effects of beta-adrenergic agonists and antagonists in LQT1, LQT2 and LQT3 models of the long QT syndrome. *J. Am. Coll. Cardiol* 2000;35:778–786. [PubMed: 10716483]
63. NODA T, TAKAKI H, KURITA T, et al. Gene-specific response of dynamic ventricular repolarization to sympathetic stimulation in LQT1, LQT2 and forms of con-genital long QT syndrome. *Eur. Heart J* 2002;23:975–983. [PubMed: 12069453]
64. SCHWARTZ PJ, PRIORI SG, SPAZZOLINI C, et al. Genotype-phenotype correlation in the long-QT syndrome: gene-specific triggers for life-threatening arrhythmias. *Circulation* 2001;103:89–95. [PubMed: 11136691]
65. ALI RH, ZAREBA W, MOSS A, et al. Clinical and genetic variables associated with acute arousal and nonarousal-related cardiac events among subjects with long QT syndrome. *Am. J. Cardiol* 2000;85:457–461. [PubMed: 10728950]
66. GUSSAKI I, BRUGADA P, BRUGADA J, et al. Idiopathic short QT interval: a new clinical syndrome. *Cardiology* 2000;94:99–102. [PubMed: 11173780]
67. GUSSAK I, BRUGADA P, BRUGADA J, et al. ECG phenomenon of idiopathic and paradoxical short QT intervals. *Cardiac. Electrophysiol. Rev* 2002;6:49–53.
68. GAITA F, GIUSTETTO C, BIANCHI F, et al. Short QT Syndrome: a familial cause of sudden death. *Circulation* 2003;108:965–970. [PubMed: 12925462]
69. BRUGADA R, HONG K, DUMAINE R, et al. Sudden death associated with short-QT syndrome linked to mutations in HERG. *Circulation* 2004;109:30–35. [PubMed: 14676148]
70. BELLOCQ C, VAN GINNEKEN A, BEZZINA CR, et al. Mutation in the KCNQ1 gene leading to the short QT-interval syndrome. *Circulation* 2004;109:2394–2397. [PubMed: 15159330]
71. EXTRAMIANA F, ANTZELEVITCH C. Transmural electrophysiological heterogeneities underlying arrhythmogenesis associated with short QT intervals. *Circulation* 2004;110:3661–3666. [PubMed: 15569843]
72. LEENHARDT A, LUCET V, DENJOY I, et al. Catecholaminergic polymorphic ventricular tachycardia in children: a 7-year follow-up of 21 patients. *Circulation* 1995;91:1512–1519. [PubMed: 7867192]
73. SWAN H, PIIPPO K, VIITASALO M, et al. Arrhythmic disorder mapped to chromosome 1q42-q43 causes malignant polymorphic ventricular tachycardia in structurally normal hearts. *J. Am. Coll. Cardiol* 1999;34:2035–2042. [PubMed: 10588221]
74. PRIORI SG, NAPOLITANO C, MEMMI M, et al. Clinical and molecular characterization of patients with catecholaminergic polymorphic ventricular tachycardia. *Circulation* 2002;106:69–74. [PubMed: 12093772]
75. PRIORI SG, NAPOLITANO C, TISO N, et al. Mutations in the cardiac ryanodine receptor gene (hRyR2) underlie catecholaminergic polymorphic ventricular tachycardia. *Circulation* 2001;103:196–200. [PubMed: 11208676]
76. LAITINEN PJ, BROWN KM, PIIPPO K, et al. Mutations of the cardiac ryanodine receptor (RyR2) gene in familial polymorphic ventricular tachycardia. *Circulation* 2001;103:485–490. [PubMed: 11157710]
77. POSTMA AV, DENJOY I, HOORNTJE TM, et al. Absence of calsequestrin 2 causes severe forms of catecholaminergic polymorphic ventricular tachycardia. *Circ. Res* 2002;91:e21–e26. [PubMed: 12386154]

78. NAM GB, BURASHNIKOV A, ANTZELEVITCH C. Cellular mechanisms under-lying the development of catecholaminergic ventricular tachycardia. *Circulation*. 2004In press