研究成果の刊行に関する一覧表

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Shimizu W, Matsuo K, Kokubo Y, Satomi K, Kurita T, Noda T, Nagaya N, Suyama K, Aihara N, Kamakura S, Inamoto N, Akahoshi M, Tomoike H	Sex hormone and gender difference. Role of testosterone on male predominance in Brugada syndrome.	J Cardiovasc Electrophysiol	18	415-421	2007
Shimizu W, Aiba T, Kamakura S	Mechanism and new findings in Brugada syndrome.	Circ J	71	A32-A39	2007
Moss AJ*, Shimizu W*, Wilde AAM*, Towbin JA*, Zareba Z, Robinson JL, Qi M, Vincent GM, Ackerman MJ, Kaufman ES, Hofman N, Seth R, Kamakura S, Miyamato Y, Goldenberg I, Andrews ML, McNitt S	Clinical aspects of type-1 long-QT syndrome by location, coding type, and biophysical function of mutations involving the KCNQ1 gene.	Circulation	115	2481-2489	2007 * These 4 authors Equally contributed
Miyamoto K, Yokokawa M, Tanaka K, Nagai T, Okamura H, Noda T, Satomi K, Suyama K, Kurita T, Aihara N, Kamakura S, Shimizu W	Diagnostic and prognostic value of type 1 Brugada electrocardiogram at higher (third or second) V1 to V2 recording in men with Brugada syndrome.	Am J Cardiol	99	53-57	2007
Ohgo T, Okamura H, Noda T, Satomi K, Suyama K, Kurita T, Aihara N, Kamakura S, Ohe T, Shimizu W	Acute and chronic management in patients with Brugada syndrome associated with electrical storm of ventricular fibrillation.	Heart Rhythm	4	695-700	2007
Yokokawa M, Noda T, Okamura H, Satomi K, Suyama K, Kurita T, Aihara N, Kamakura S, Shimizu W	Comparison of long-term follow-up of electrocardiographic features in Brugada syndrome between the SCN5 A-positive probands and the SCN5A-negative probands.	Am J Cardiol	100	649-655	2007
Crotti L, Spazzolini C, Schwartz PJ, Shimizu W, Denjoy I, Schulze-Bahr E, Zaklyazminskaya EV, Swan H, Ackerman MJ, Moss AJ, Wilde AM, Horie M, Brink PA, Insolia R, De Ferrari GM, Crimi G	The common long QT syndrome mutation KCNQ1/A341V causes unusually severe clinical manifestations in patients with different ethnic backgrounds: Toward a mutation-specific risk stratification.	Circulation	116	2366-2375	2007
Horigome H, Iwashita H, Yoshinaga M, Shimizu W	Magnetocardiographic demonstration of torsade de pointes in a fetus with congenital long QT syndrome.	J Cardiovasc Electrophysiol	19	334-335	2008
Sumitomo N, Shimizu W, Taniguchi K, Hiraoka M	Ca^{2+} channel blocker and adenosine triphosphate terminate bidirectional ventricular tachycardia in a patient with Andersen-Tawil syndrome.	Heart Rhythm	5	498-499	2008
Nagaoka I, Shimizu W, Itoh H, Yamamoto S, Sakaguchi T, Oka Y, Tsuji K, Ashihara T, Ito M, Yoshida H, Ohno S, Makiyama T, Miyamoto Y, Kamakura S, Akao M, Horie M	Mutation site dependent variability of cardiac events in Japanese LQT2 form of congenital long-QT syndrome.	Circ J			2008 (in press)
Sakaguchi T, Shimizu W, Itoh H, Noda T, Miyamoto Y, Nagaoka I, Ashihara T, Ito M, Tsuji K, Ohno S, Makiyama T, Kamakura S, Horie M	Age-related triggers for life-threatening arrhythmia in the genotyped long-QT syndrom.	J Cardiovasc Electrophysiol			2008 (in press)

清水　渉, 柴田季子, 山下菜津子, 太田直孝, 浦　敏郎, 宮本恵宏, 吉政康直, 鎌倉史郎	チャネル病と遺伝子多型	心臓	39	586-591	2007
清水　渉	Brugada症候群の性差、人種差、治療	「Brugada症候群の治療」		1-6	2007
清水　渉	トピックス. Brugada症候群・QT延長症候群の治療戦略	Modern Physician	27	111-116	2007
清水　渉	学術、Brugada症候群の診断と治療	日本医事新報	4338	57-62	2007
清水　渉	突然死をきたす遺伝性不整脈の最近の話題	臨床と研究	84	129-132	2007
宮本康二, 清水　渉	2. Brugada症候群の心電図診断. b.高位肋間心電図、負荷心電図. 特集「Brugada症候群 - 解明された病態に基づいた診断と治療 -」	Heart View	11	22-28	2007
野田　崇, 清水　渉	第6回 U波が異常な波形	Circulation Up-to-Date	2	94-98	2007
清水　渉	遺伝情報に基づいた先天性QT延長症候群の管理と治療	日本小児循環器学会雑誌	24	27-33	2008
清水　渉, 相庭武司, 栗田隆志, 里見和浩, 横川美樹, 岡村英夫, 野田　崇, 須山和弘, 相原直彦, 鎌倉史郎	Brugada症候群における性差と加齢	心電図	27		2008 (印刷中)
Tsujita Y, Nakamura Y, Zhang Q, Tamaki S, Nozaki A, Amamoto K, Kadowaki T, Kita Y, Okamura T, Horie M, Ueshima H	The association between high-density lipoprotein cholesterol level and cholesteryl ester transfer protein taqIB gene polymorphism is influenced by alcohol drinking in a population-based sample.	Atherosclerosis	191	199-205	2007
Toda H, Ding WG, Yasuda Y, Toyoda F, Ito M, Matsuura H, Horie M	Stimulatory action of protein kinase Cvarepsilon isoform on the slow component of delayed rectifier K(+) current in guinea-pig atrial myocytes.	Br J Pharmacol	150	1011-1021	2007
Itoh H, Tsuji K, Sakaguchi T, Nagaoka I, Oka Y, Nakazawa Y, Yao T, Jo H, Ashihara T, Ito M, Horie M, Imoto K	A paradoxical effect of lidocaine for the N406S mutation of SCN5A associated with Brugada syndrome.	Int J Cardiol	121	249-252	2007
Horie M, Ito H	Disorders of cardiac repolarization-long QT and short QT syndromes-.	Circ J	71	A50-53	2007
Sumitomo N, Sakurada H, Taniguchi K, Matsumura M, Abe O, Miyashita M, Kanamaru H, Karasawa K, Ayusawa M, Fakamizu S, Nagaoka I, Horie M, Harada K, Hiraoka M	Association of atrial arrhythmia and sinus node dysfunction in patients with catecholaminergic polymorphic ventricular tachycardia.	Circ J	71	1606-1609	2007
堀江　稔	家族性心房細動を識る	Heart View	11	84-86	2007
道智賢市, 松本祐一, 長岡伊織, 伊藤　誠, 芦原貴司, 伊藤英樹, 八尾武憲, 坂口知子, 中澤優子, 岡　優子, 辻　啓子, 堀江　稔	心筋リアノジン受容体の遺伝子変異（I4587V）を有したカテコラミン誘発性多形性心室頻拍の１成人症例	心電図	27	246-252	2007
堀江　稔	Jervell and Lange-Nielsen症候群	日本臨床	別冊4	205-208	2007
Yada H, Murata M, Shimoda K, Yuasa S, Kawaguchi H, Ieda M, Adachi T, Murata M, Ogawa S, Fukuda K	Dominant negative suppression of Rad leads to QT prolongation and causes ventricular arrhythmias via modulation of L-type calcium current in the heart.	Circ Res	101	69-77	2007

Ieda M, Kanazawa H, Kimura K, Hattori F, Ieda Y, Taniguchi M, Lee JK, Matsumura K, Tomita Y, Miyoshi S, Shimoda K, Makino S, Sano M, Kodama I, Ogawa S, Fukuda K	Sema3 maintains normal heart rhythm through sympathetic innervations Patterning.	Nat Med	13	604-612	2007
Hagiwara S, Miyoshi S, Fukuda K, Nishiyama N, Ikegami Y, Tanimoto K, Murata M, Takahashi E, Shimoda K, Hirano T, Mitamura H, Ogawa S	SHP2-mediated singaling cascade through gp130 is essential for LIF-dependent $I_{Ca,L}$, $[Ca^{2+}]_i$, and APD increase in cardiomyocytes.	J Mol Cell Cardiol	43	710-716	2007
Aizawa Y, Ueda K, Scornik F, Cordeiro JM, Wu Y, Desai M, Guerchicoff A, Nagata Y, Iesaka Y, Kimura A, Hiraoka M, Antzelevitch C	A novel mutation in KCNQ1 associated with a potent dominant negative effect as the basis for the LQT1 form of the long QT syndrome.	J Cardiovasc Electrophysiol	18	972-7	2007
Chinushi M,Komura S,Izumi D, Furushima H,Tanabe Y, Washizuka T,Aizawa Y	Incidence and Initial Characteristics of Pilsicainide-Induced Ventricular Arrhythmias in Patients With Brugada Syndrome.	PACE	30	662-671	2007
Furushima H, Chinushi M, Okamura K, Iijima K, Komura S, Tanabe Y, Okada S, Izumi D, Aizawa Y	Comparison of conduction delay in the right ventricular outflow tract between Brugada syndrome and right ventricular cardiomyopathy: investigation of signal average ECG in the precordial leads.	Europace	9	951-6	2007
Chinushi M, Izumi D, Iijima K, Ahara S, Komura S, Furushima H, Hosaka Y, Aizawa Y	Antiarrhythmic vs. pro-arrhythmic effects depending on the intensity of adrenergic stimulation in a canine anthopleurin-A model of type-3 long QT syndrome.	Europace	10	249-55	2008
Haissaguerre M, Aizawa Y, Sacher F, Pasquie JL, Nogami A, Tli-Mayry S, Matsuo S, Probst V, Le Scouarnec S, Takahashi Y, Hochini M, Veenhuzen G, Derval N, Knecht S, Arantes L, Bordachar P, Sanders P, Jais P, Klein GJ, Clementy J	Sudeen cardiac death associated with repolarization abnormality.	N Engl J Med			2008 (in press)
Ikrar T, Hanawa H, Watanabe H, Okada S, Aizawa Y, Ramadan MM, Komura S, Yamashita F, Chinushi M, Aizawa Y	A double-point mutation in the selectivity filter site of the KCNQ1 potassium channel results in a severe phenotype, LQT1, of long QT syndrome.	J Cardiovasc Electrophysiol			2008 (in press)
Aizawa Y, Tagawa M, Chinushi M, Furushima, H, Watanabe H. and Komura A	Post-QRS potential in Brugada syndrome: its relation to ECG pattern and possible genesis.	J Am Coll Cardiol			2008 (in press)
Nakamura K, Katayama Y, Kusano FK, Haraoka K, Tani Y, Nagase S, Morita H, Miura D, Fujimoto Y, Furukawa T, Ueda K, Aizawa Y, Kimura A, Kurachi Y, Ohe T	Anti-KCNH2 antibody-induced long QT syndrome -Novel acquired form of LQT syndrome-.	J Am Coll Cardiol	50	1808-1809	2007
Tani Y, Miura D, Kurokawa J, Nakamura K, Ouchida M, Shimizu K, Ohe T, Furukawa T	T75M-KCNJ2 mutation causing Andersen-Tawil syndrome enhances inward rectification by changing Mg(2+) sensitivity.	J Mol Cell Cardiol	43	187-196	2007

Nagase S, Kusano KF, Yoshida M, Ohe T	Electrophysiologic characteristics of an Andersen syndrome patient with KCNJ2 mutation.	Heart Rhythm	4	512-515	2007
Kusano KF, Taniyama M, Nakamura K, Miura D, Banba K, Nagase S, Morita H, Nishii N, Watanabe A, Tada T, Murakami M, Miyaji K, Hiramatsu S, Nakagawa K, Tanaka M, Miura A, Kimura H, Fuke S, Sumita W, Urakawa S, Iwasaki J, Ohe T	Atrial fibrillation in patients with Brugada syndrome - relationships of gene mutation, electrophysiology and clinical backgrounds -.	J Am Coll Cardiol	51	1169-1175	2008
Nagase S, Kusano KF, Morita H, Nishii N, Banba K, Watanabe A, Hiramatsu S, Nakamura K, Sakuragi S, Ohe T	Longer repolarization in the epicardium at the right ventricular outflow tract. Causes type 1 ECG in patients with Brugada syndrome.	J Am Coll Cardiol	51	1154-1161	2008
森田志保, 大江 透	QT延長症候群.	Pharma Medica	25	59-62	2007
Takeda Y, Zhu A, Yoneda T, Usukura M, Takata H, Yamagishi M	Effects of aldosterone and angiotensin II receptor blockade on cardiac angiot ensinogen and angiotensin-converting e nzyme 2 expression in Dahl salt-sensit ive hypertensive rats.	Am J Hypertens	10	1119-24	2007
Katsuda Y, Asano A, Murase Y, Chujo D, Yagi K, Kobayashi J, Mabuchi H, Yamagishi M	Association of genetic variation of the adiponectin gene with body fat distrib ution and carotid atherosclerosis in Jap anese obese subjects.	J Atheroscler Thromb	1	19-26	2007
Nohara A, Kawashiri MA, Claudel T, Mizuno M, Tsuchida M, Takata M, Katsuda S, Miwa K, Inazu A, Kuipers F, Kobayashi J, Koizumi J, Yamagishi M, Mabuchi H	High frequency of a retinoid X receptor gamma gene variant in familial combined hyperlipidemia that associates with atherogenic dyslipidemia.	Arterioscler Thromb Vasc Biol	4	923-8	2007
Konno T, Fujino N, Hayashi K, Uchiyama K, Masuta E, Katoh H, Sakamoto Y, Tsubokawa T, Ino H, Yamagishi M	Differences in the diagnostic value of various criteria of negative T waves for hypertrophic cardiomyopathy based on a molecular genetic diagnosis.	Clin Sci (Lond)	112	577-82	2007
Kaneda T, Naruse C, Kawashima A, Fujino N, Oshima T, Namura M, Nunoda S, Mori S, Konno T, Ino H, Yamagishi M, Asano M	A novel beta-myosin heavy chain gene mutation, p.Met531Arg, identified in is olated left ventricular noncompaction in humans, resulted in left ventricular hypertrophy that progressed to dilation in a mouse model.	Clin Sci (Lond)	114	431-440	2008
Sakata K, Ino H, Fujino N, Nagata M, Uchiyama K, Hayashi K, Konno T, Inoue M, Kato H, Sakamoto Y, Tsubokawa T, Yamagishi M	Exercise-induced systolic dysfunction in patients with non-obstructive hypertrophic cardiomyopathy and mutations in the cardiac troponin genes.	Heart			2008 (in press)
Kawashiri MA, Nohara A, Tada H, Mori M, Tsuchida M, Katsuda S, Inazu A, Kobayashi J, Koizumi J, Mabuchi H, Yamagishi M	Comparison of effects of pitavastatin and atorvastatin on plasma coenzyme Q10 in heterozygous familial hypercholesterolemia: Results from a crossover study.	Clin Pharmacol Ther			2008 Oct 24. (in press)
Makita N, Sumitomo N, Watanabe I, Tsutsui H	Novel SCN5A mutation (Q55X) associated with age-dependent expression of Brugada syndrome presenting as neurally mediated syncope.	Heart Rhythm	4	516-519	2007

Makita N, Tsutsui H	Genetic polymorphisms and arrhythmia susceptibility.	Circ J	71	A54-A60	2007
Shan L, Makita N, Xing Y, Watanabe S, Futatani T, Ye F, Saito K, Ibuki K, Watanabe K, Hirono K, Uese K, Ichida F, Miyawaki T, Origasa H, Bowles NE, Towbin JA	SCN5A variants in Japanese patients with left ventricular noncompaction an d arrhythmia.	Mol Genet Metabol	93	468-474	2007
蒔田直昌, 佐々木孝治, 筒井裕之	「Brugada症候群の病因と発生機序」	心臓	39	4-9	2007
蒔田直昌	「不整脈のハプロタイプ解析と人種差」	心電図	27	S3 3-14	2007
蒔田直昌, 筒井裕之	「不整脈で見られる遺伝子異常」	臨床検査	51	691-696	2007
蒔田直昌, 佐々木孝治, 清水渉, 堀江 稔	遺伝子多型と臨床薬理 致死性不整脈の遺伝子基盤に関するイオンチャネルのゲノム薬理学的研究 イオンチャネルの遺伝子多型と致死性不整脈	臨床薬理の進歩		8-14	2007
Mio F, Chiba K, Hirose Y, Kawaguchi Y, Mikami Y, Oya T, Mori M, Kamata M, Matsumoto M, Ozaki K, Tanaka T, Takahashi A, Kubo T, Kimura T, Toyama Y, Ikegawa S	A functional polymorphism in COL11A1, Which encodes the alpha 1 chain of type XI collagen, is associated with susceptibility to lumbar disc herniation.	American Journal of Human Genetics	81	1271-1277	2007
The International HapMap Consortium	Genome-wide detection and characterization of positive selection in human populations.	Nature	449	913-918	2007
The International HapMap Consortium	A second generation human haplotypemap of over 3.1 million SNPs.	Nature	449	851-861	2007
Miyamoto Y, Mabuchi A, Shi D, Kubo T, Takatori Y, Saito S, Fujioka M, Sudo A, Uchida A, Yamamoto S, Ozaki K, Takigawa M, Tanaka T, Nakamura Y, Jiang Q, Ikegawa S	A functional polymorphism in the 5' UTR of GDF5 is associated with susceptibility to osteoarthritis.	Nature Genetics	39	529-533	2007
Ebana Y, Ozaki K, Inoue K, Sato H, Iida A, Lwin H, Saito S, Mizuno H, Takahashi A, Nakamura T, Miyamoto Y, Ikegawa S, Odashiro K, Nobuyoshi M, Kamatani N, Hori M, Isobe M, Nakamura Y, Tanaka T	A functional SNP in ITIH3 is associated with susceptibility to myocardial infarction.	Journal of Human Genetics	52	220-229	2007
Tsuji K, Akao M, Ishii TM, Ohno S, Makiyama T, Takenaka K, Doi T, Haruna Y, Yoshida H, Nakashima T, Kita T, Horie M	Mechanistic basis for the pathogenesis of long QT syndrome associated with a common splicing mutation in KCNQ1 gene.	J Mol Cell Cardiol	42	662-9	2007
Ohno S, Zankov DP, Yoshida H, Tsuji K, Makiyama T, Itoh H, Akao M, Hancox JC, Kita T, Horie M	N- and C-terminal KCNE1 mutations cause distinct phenotypes of long QT syndrome.	Heart Rhythm	4	332-40	2007
Haruna Y, Kobori A, Makiyama T, Yoshida H, Akao M, Doi T, Tsuji K, Ono S, Nishio Y, Shimizu W, Inoue T, Murakami T,	Genotype-phenotype correlations of KCNJ2 mutations in Japanese patients with Andersen-Tawil syndrome.	Hum Mutat	28	208	2007

Tsuboi N, Yamanouchi H, Ushinohama H, Nakamura Y, Yoshinaga M, Horigome H, Aizawa Y, Kita T, Horie M					
Akao M, Takeda T, Kita T, Kume T, Akaike A	Serofendic acid, a substance extracted from fetal calf serum, as a novel drug for cardioprotection.	Cardiovasc Drug Rev	25	333-41	2007
牧山　武, 赤尾昌治, 伊藤英樹, 堀江　稔	Brugada症候群と遺伝子病 (Brugada症候群とQT延長症候群等他の遺伝子病との関連について)	Heart View	11	54-61	2007
Shimasaki Y, Saito Y, Yoshimura M, Kamitani S, Miyamoto Y, Masuda I, Nakayama M, Mizuno Y, Ogawa H,Yasue H, Nakao K	The effects of long-term smoking on endothelial nitric oxide synthase mRNA expression in human platelets as detected with real-time quantitative RT-PCR.	Clinical and applied thrombosis/ hemostasis	13	43-51	2007
Ito A, Suganami T, Miyamoto Y, Yoshimasa Y, Takeya M, Kamei Y, Ogawa Y	Role of MAPK phosphatase-1 in the induction of monocyte chemoattractant protein-1 during the course of adipocyte hypertrophy.	J Biological Chemistry	282	25445-25452	2007
Nishijima T, Nakayama M, Yoshimura M, Abe K, Yamamuro M, Suzuki S, Shono M, Sugiyama S, Saito Y, Miyamoto Y, Nakao K, Yasue H, Ogawa H	The endothelial nitric oxide synthase gene -786T/C polymorphism is a predictive factor for reattacks of coronary spasm.	Phamacogenet Genomics	17	581-587	2007

Ⅳ. 研究成果の刊行物・別刷り

28
Provocative Testing in Inherited Arrhythmias

Wataru Shimizu and Michael J. Ackerman

Introduction

Heritable channelopathies that include congenital long QT syndrome (LQTS), Brugada syndrome (BrS), and catecholaminergic polymorphic ventricular tachycardia (CPVT) affect an estimated 1 in 2000 persons, may present with syncope or sudden cardiac death, and often elude detection by standard 12-lead electrocardiography (ECG). In LQTS, an estimated 40% of genetically affected subjects have "concealed" LQTS with a normal or borderline heart rate corrected QT interval (QTc) at rest. A significant proportion of patients with BrS has concealed BrS with no evidence of a type 1 Brugada electrocardiographic pattern at rest. Every patient with CPVT has a normal resting ECG. Provocative testing with catecholamines and pharmacological testing with sodium channel blockers are critical diagnostic tests in the evaluation of these channelopathies and can help unmask LQTS, BrS, and CPVT in their concealed state. The role of these provocative tests in the evaluation of inherited arrhythmia syndromes will be reviewed in this chapter.

Congenital Long QT Syndrome

Congenital LQTS is characterized by QT prolongation in the electrocardiogram (ECG) and its trademark dysrhythmia of polymorphic ventricular tachycardia known as torsade de pointes (TdP).[1] The clinical diagnosis of LQTS is mainly based on the resting QTc, cardiac events such as syncope, aborted cardiac arrest, and sudden cardiac death, and a family history of apparent LQTS.[2] However, the electrocardiographic diagnosis at baseline has long been expected to miss some patients affected by congenital LQTS (so called concealed LQTS) as evidenced by syncopal events occurring among family members with a "normal" QT interval.[3] Since 1995, when the first two genes responsible for LQTS were identified, molecular genetic studies have revealed a total of 10 forms of congenital LQTS caused predominantly by cardiac channel mutations or mutations involving key β or auxiliary subunits.[4] Among the 10 genetic subtypes, LQT1, LQT2, and LQT3 constitute the majority of genotyped LQTS and approximately 75% of all LQTS.[5] With these molecular illuminations, this entity of concealed or low pentrant LQTS has been proved genetically. Vincent *et al.* reported that 5 (6%) of 82 mutation carriers from three LQT1 families had a normal QT interval.[6] Priori *et al.* conducted molecular screening in nine families with apparently sporadic cases of LQTS, demonstrating a very low penetrance (38%, 9/24 patients).[7] Swan and co-workers reported that the sensitivity and specificity for identifying genotype-positive patients were 53 and 100%, respectively, in an LQT1 family with a specific *KCNQ1* mutation (D188N).[8] More recently, a large study of genotyped LQTS by Priori *et al.* showed that the percentage of genetically affected patients with a normal QTc was significantly higher in the LQT1 (36%) than in the LQT2 (19%) or the LQT3 (10%) syndromes.[9] Overall, these findings strongly suggest the need for novel tools to unveil concealed mutation carriers of LQTS, especially those

with type 1 LQTS (LQT1). The identification of patients with concealed LQTS affords the opportunity to initiate potentially life-saving pharmacotherapies and healthstyle modifications.

Many but not all patients with congenital LQTS suffer from cardiac events such as syncope and/or sudden cardiac death during physical exercise or mental stress. Therefore, provocative testing using catecholamine infusion or exercise has long been used to unmask concealed forms of congenital LQTS, before genetic screening became available.[10]

The Epinephrine QT Stress Test in Long QT Syndrome

Infusion of isoproterenol, a β-adrenergic agonist, or epinephrine, an α + β-adrenergic agonist, has been reported to be useful as a provocative test in LQTS more than two decades ago.[10] The heart rate is usually increased to more than 100 beats/min by isoproterenol, especially by the use of a bolus injection, which often makes it difficult to measure the QT interval precisely due to an overlap of the next P wave on the terminal portion of the T wave. Prior to the discovery of the distinct genetic subtypes of LQTS, the responses to either epinephrine or isoproterenol were extremely heterogeneous and were deemed impossible to interpret; as a result, epinephrine QT stress testing disappeared from the diagnostic work-up of LQTS. Now, however, the heterogeneous response is understood to stem from the underlying genetic heterogeneity and the gene-specific responses to epinephrine can be exploited to expose different types of LQTS in its otherwise concealed state, particularly type 1 LQTS (LQT1). Although isoproterenol is still used occasionally, recent major insights have been gleaned from using epinephrine and are reviewed in more detail below. In contrast to provocation studies using catecholamines, Viskin and colleagues have shown that sudden heart rate oscillations precipitated by intravenous administration of adenosine may expose some patients with concealed LQTS, although genotype-specific responses have not been demonstrated.[11] Compared to controls, patients with LQTS exhibited an exaggerated increase in the QT interval during adenosine-induced bradycardia.

The two major protocols developed for epinephrine QT stress testing include the escalating-dose protocol by Ackerman's group (the Mayo protocol)[12] and the bolus injection followed by brief continuous infusion by Shimizu's group (Shimizu protocol).[13] Both protocols are extremely useful and safe, and overall are well tolerated. Each protocol has some advantages and disadvantages with respect to the other.

Incremental, Escalating Epinephrine Infusion (Mayo Protocol)

Ackerman and co-workers have used a 25-min incremental, escalating infusion protocol (0.025–0.3 μg/kg/min) in the LQT1, LQT2, and LQT3 patients and in the genotyped-negative patients (Figure 28–1A).[12,14,15] With epinephrine infusion at a low dose of ≤0.1 μg/kg/min, the median change of the QT interval was 78 msec in LQT1, −4 msec in LQT2, −58 msec in LQT3, and −23 msec in the genotype-negative patients (Figure 28–1B). They found a paradoxic QT prolongation, defined as a 30-msec increase in the QT (not QTc) interval during low-dose epinephrine infusion, specific in the LQT1 patients (92%), but not in the LQT2 (13%), the LQT3 (0%), and the genotype-negative patients (18%). The paradoxic QT prolongation had a sensitivity of 92.5%, specificity of 86%, positive predictive value of 76%, and negative predictive value of 96% for LQT1 vs. non-LQT1 status (Table 28–1), and provides a presumptive, pregenetic clinical diagnosis of type 1 LQTS (LQT1).

The major advantages of this escalating infusion protocol are better patient tolerance and a lower incidence of false-positive responses. On the other hand, this protocol seems less effective in exposing patients with LQT2 compared to the bolus protocol by Shimizu *et al.* described below. However, this disadvantage is reported to be partially overcome by focusing on the change of T wave morphology during low-dose epinephrine infusion. Khositseth *et al.* reported that the epinephrine-induced notched T wave was more indicative of LQT2 status.[15]

Bolus Injection followed by Brief Continuous Infusion (Shimizu Protocol)

The bolus protocol by Shimizu and co-workers was developed on the basis of a differential

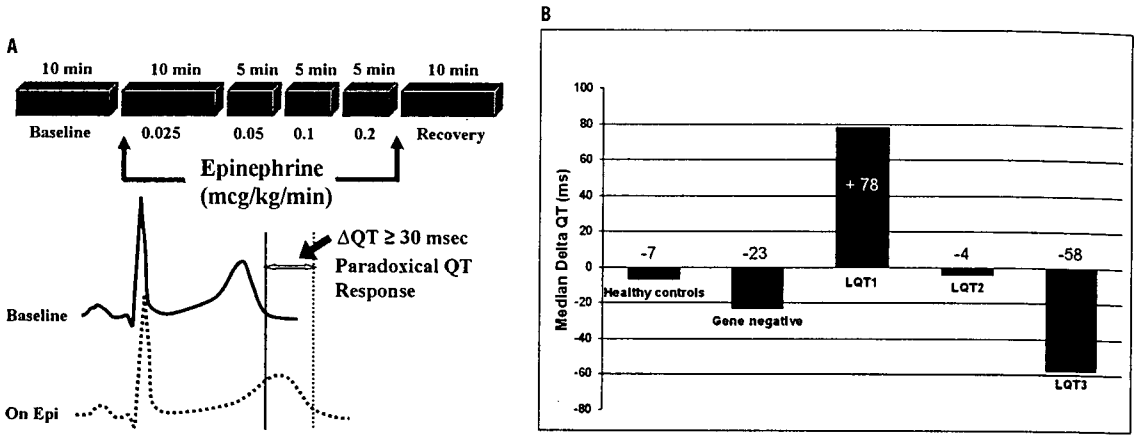

FIGURE 28–1. Epinephrine QT stress testing in LQTS (Mayo protocol). (A) Schematic of the epinephrine infusion protocol used to unmask concealed type 1 long QT syndrome (LQT1). With this protocol, the paradoxic response is defined as an increase in the absolute QT interval by ≥30 msec during infusion of low-dose epinephrine (≤0.1 μg/kg/min). (B) Summary of the low-dose epinephrine-absolute QT response performed in over 200 subjects at the Mayo Clinic.

response of action potential duration (APD) and QT interval to sympathetic stimulation with isoproterenol between the experimental LQT1, LQT2, and LQT3 models employing arterially perfused canine left ventricular wedge preparations.[16] Persistent prolongation of the APD and QT interval at steady-state conditions of isoproterenol infusion was reported in the LQT1 model. Under normal conditions, β-adrenergic stimulation is expected to increase the net outward repolarizing current due to a larger increase of outward currents, including the Ca^{2+}-activated slow component of the delayed rectifier potassium current (I_{Ks}) and the Ca^{2+}-activated chloride current ($I_{Cl(Ca)}$), than that of an inward current, the Na^+/Ca^{2+} exchange current ($I_{Na\text{-}Ca}$), resulting in an abbreviation of APD and the QT interval. A defect in I_{Ks} as seen in LQT1 could account for failure of β-adrenergic stimulation to abbreviate APD and the QT interval, resulting in a persistent and paradoxic QT prolongation under sympathetic stimulation. In the LQT2 model, isoproterenol infusion was reported to initially prolong but then abbreviate APD and the QT interval probably due to an initial augmentation of $I_{Na\text{-}Ca}$ and a subsequent stimulation of I_{Ks}. In contrast to the LQT1 and LQT2 models, isoproterenol infusion constantly abbreviated APD and the QT interval as a result of a stimulation of I_{Ks} in the LQT3 model, because an inward late I_{Na} was augmented in this genotype. Therefore, the bolus protocol of epinephrine testing was expected not only to unmask concealed patients with LQTS but also to presumptively diagnose the three most common subtypes, LQT1, LQT2, and LQT3, by monitoring the temporal course of the QTc to epinephrine at peak effect following bolus injection and at steady-state effect during continuous infusion.

TABLE 28–1. Validity of the epinephrine QT stress test (Mayo protocol) at a QT ≥ 30 msec.

ΔQT[a]	LQT1	Non-LQT1	Predictive value
ΔQT ≥ 30 msec	37	12	Positive predictive value = 76%
ΔQT < 30 msec	3	73	Negative predictive value = 96%
	Sensitivity = 92.5%	Specificity = 86%	

[a]Δ, the change (delta) in the QT interval (epinephrine minus baseline).

Clinical data using the bolus protocol suggested that sympathetic stimulation produces genotype-specific responses of the QTc interval in patients with LQT1, LQT2, and LQT3 (Figure 28–2).[17,18] Epinephrine remarkably prolonged the QTc interval at peak effect when the heart rate is maximally increased (1–2 min after the bolus injection), and the QTc remained prolonged during steady-state epinephrine effect (3–5 min) in patients with LQT1.[17,18] As an aside, this steady-state effect likely correlates with the paradoxic QT response seen with the Mayo protocol. The QTc was also prolonged at peak epinephrine effect (during bolus)

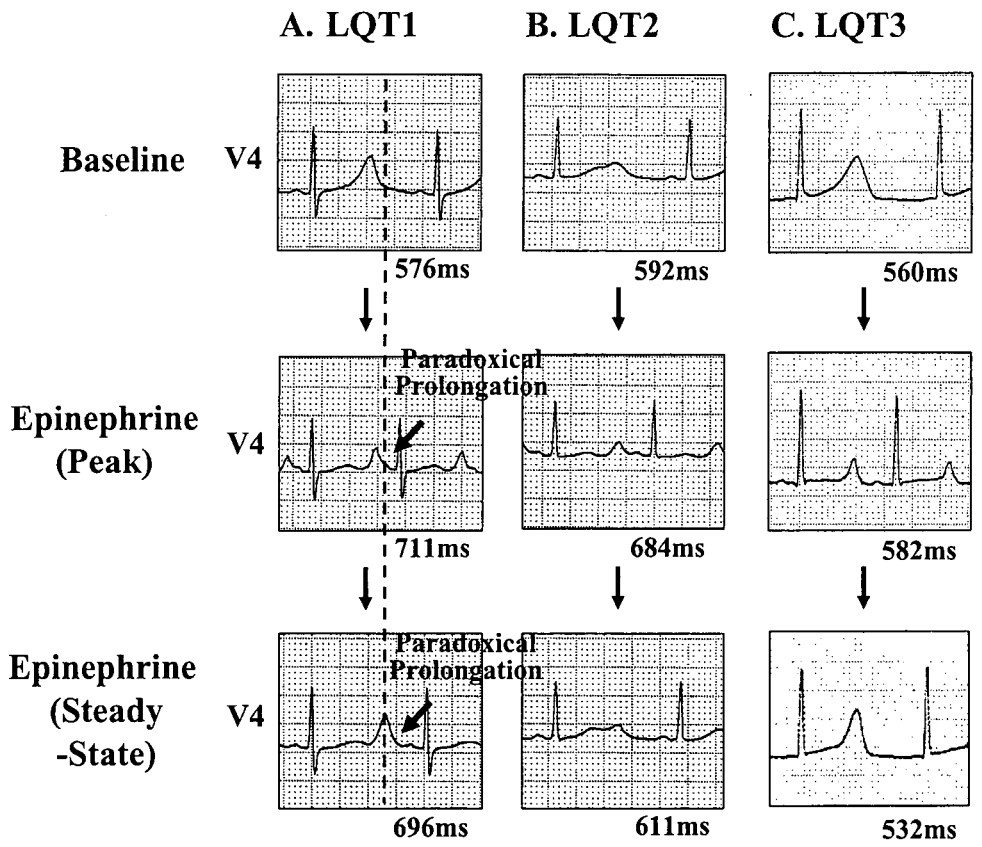

FIGURE 28–2. Differential temporal course of the heart rate corrected QT interval (QTc) to epinephrine QT stress testing in LQT1, 2, and 3 (Shimizu protocol). The V4 lead ECGs under baseline conditions and at peak and steady-state epinephrine effects in LQT1 (A), LQT2 (B), and LQT3 (C) patients using the Shimizu bolus and infusion protocol are shown. The corrected QT interval (QTc) was prominently prolonged from 576 to 711 msec at peak epinephrine effect, and remained prolonged at steady state (696 msec) in the patient with LQT1. It is noteworthy that paradoxic QT prolongation was seen both at peak and steady-state epinephrine effects (arrows). In the patient with LQT2, the QTc was also dramatically prolonged from 592 to 684 msec at peak, but returned to the baseline level at steady state (611 msec). It was much less prolonged (560 to 582 msec) at peak in the LQT3 patient than in either the LQT1 or LQT2 patient, and returned below the baseline level at steady state (532 msec).

in patients with LQT2, but returned to close to baseline levels at the steady-state epinephrine effect.[18] In contrast, the QTc was less prolonged at the peak epinephrine effect in the LQT3 patients than in the LQT1 or LQT2 patients, and was abbreviated below baseline levels at the steady-state epinephrine effect.[18] The responses of the corrected T_{peak}–T_{end} interval reflecting transmural dispersion of repolarization (TDR) approximately paralleled those of the QT interval,[19] supporting the cellular basis for genotype-specific triggers for cardiac events.

By using the steady-state epinephrine effect, Shimizu *et al.* reported an improvement in clinical electrocardiographic diagnosis (sensitivity) from 68% to 87% in the 31 patients with LQT1 and from 83% to 91% in the 23 patients with LQT2, but not in the 6 patients with LQT3 (from 83% to 83%).[18] The bolus protocol of epinephrine effectively predicts the underlying genotype of the LQT1, LQT2, and LQT3 (Figure 28–3).[18] The prolongation of QTc ≥35 msec at steady-state epinephrine effect could differentiate LQT1 from LQT2, LQT3, or control patients with a predictive accuracy ≥90 %. The prolongation of QTc ≥80 msec at peak epinephrine effect could differentiate LQT2 from LQT3 or control patients with a predictive accuracy of 100%.

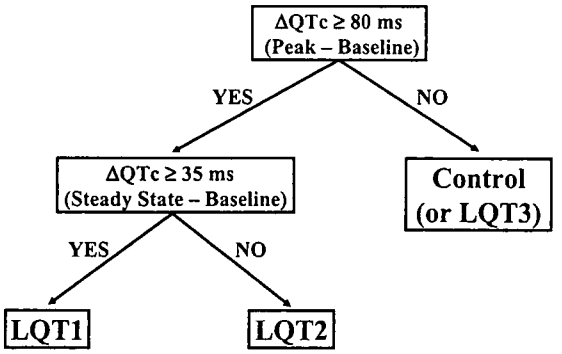

FIGURE 28–3. A flow chart to predict genotype with epinephrine QT stress testing (Shimizu Protocol).

Whether utilizing the Mayo protocol or the Shimizu protocol, the responses to epinephrine should be viewed as diagnostic only, not prognostic. Induction of TdP or ventricular fibrillation is extremely uncommon. In over 400 studies conducted using the Mayo protocol and the Shimizu protocol respectively, we have observed only two episodes of TdP (10 beats and 20 beats) and one episode of macroscopic T wave alternans. In addition, these gene-specific responses are attenuated by β blockers. If a patient displays, epinephrine-induced bradycardia rather than the expected increase in heart rate, then the study should be terminated, a diagnostic interpretation should not be rendered, and a period of monitored beta blocker washout should be considered.

Importantly, the diagnostic profiles gleaned from one protocol should *not* be applied to the other protocol. For example, using the Mayo protocol, we have observed healthy volunteers display a QTc of 600 msec (ΔQTc = 140 msec) during epinephrine infusion due to a negligible change in the absolute QT interval but a brisk chronotropic response. This response could be viewed as either an LQT1 (steady-state) or LQT2 (peak) response if the Shimizu algorithm was erroneously applied (Figure 28–3) in the setting of the Mayo protocol (Figure 28–1A). Here, it is critical to remember that the key determinant is epinephrine-mediated changes in the QT interval for the Mayo protocol and epinephrine-mediated changes in the QTc for the Shimizu protocol. Finally, a caveat regarding epinephrine-accentuated U waves is in order as erroneous inclusion of such U waves during epinephrine infusion underlies some of the false positives.

Since molecular diagnosis is still unavailable to many institutes and requires high costs and is time consuming, a clinical diagnosis of concealed LQTS by the epinephrine QT stress test can direct proper counseling and facilitate the initiation of preventive measures such as QT drug avoidance. Furthermore, a presumptive, pregenetic diagnosis of either LQT1, LQT2, or LQT3 based upon the response to epinephrine can guide gene-specific treatment strategies. Finally, since 25% of LQTS remains genetically elusive, the identification of patients with LQTS and an LQT1-like response to epinephrine, for example, may lead to the identification of novel LQTS-causing susceptibility genes.

Brugada Syndrome

Brugada syndrome is characterized by coved-type ST-segment elevation in the right precordial electrocardiographic leads (V1–V3) and an episode of ventricular fibrillation (VF) in the absence of structural heart disease.[20] However, the ST segment elevation is dynamic and is often concealed, and is reported to be accentuated just before and after episodes of ventricular fibrillation (VF).[21] A variety of antiarrhythmic drugs and autonomic agents have been reported to provoke typical ST-segment elevation.[22] Experimental studies have suggested that an intrinsically prominent transient outward current (I_{to})-mediated action potential (AP) notch and a subsequent loss of AP dome in the epicardium, but not in the endocardium, of the right ventricular outflow tract give rise to a transmural voltage gradient, resulting in a typical ST-segment elevation in leads V1–V3.[23] Because the maintenance of the AP dome is determined by the balance of currents active at the end of phase 1 of the AP (principally I_{to} and the L-type calcium current [$I_{Ca\text{-}L}$]), any interventions that increase outward currents (e.g., I_{to}, I_{Ks}, I_{Kr}) or decrease inward currents (e.g., $I_{Ca\text{-}L}$, fast I_{Na}) at the end of phase 1 of the AP can accentuate ST-segment elevation, thus producing the Brugada phenotype.

Provocative Testing with Sodium Channel Blockers

Among the interventions above, sodium channel blockers effectively amplify or unmask ST-segment elevation, and are used as a provocative test in patients with concealed BrS showing transient or no spontaneous ST-segment elevation.[24,25] Among the sodium channel blockers, the class IC drugs (flecainide, 2 mg/kg in 10 min, iv; pilsicainide 1 mg/kg in 10 min, iv) produce the most pronounced ST-segment elevation due to strong use-dependent blocking of fast I_{Na} secondary to their slow dissociation from the sodium channels.[24] Pilsicainide, a pure class IC drug developed in Japan, seems to induce ST-segment elevation more than flecainide, which is widely used throughout the world. (Figure 28–4). Induction of ventricular arrhythmias by pilsicainide was reported to be less rare than anticipated.[26] In other words, caution should be exercised when using pilsicainide in BrS drug challenge testing because of the increased potential for false-positive responses. Further studies with genetic data as the golden standard will be required to evaluate the true sensitivity and specificity of the provocative testing with each sodium channel blocker. Class IA antiarrhythmic drugs (ajmaline, procainamide, disopyramide, cibenzoline, etc.), which exhibit less use-dependent block of fast I_{Na} due to faster

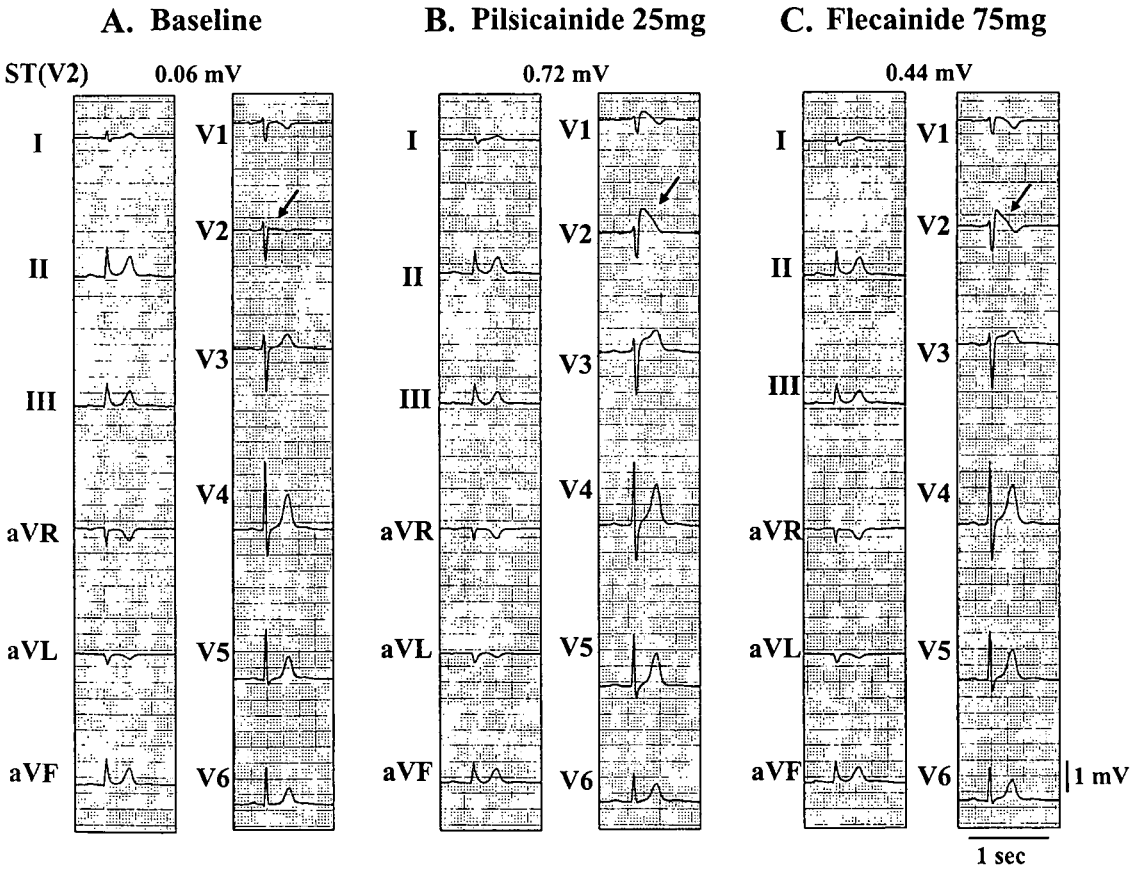

FIGURE 28–4. Effects of class IC sodium channel blockers on the ST segment in a patient with concealed Brugada syndrome. At baseline condition (A, arrow), no significant ST-segment elevation in leads V1–V3 was observed. Both pilsicainide (B, arrow) and flecainide (C, arrow) induced Type 1 coved ST-segment elevation; however, a smaller dose of pilsicainide injection (25 mg) produced more prominent ST-segment elevation than that by flecainide injection (75 mg) in lead V2 (0.72 vs. 0.44 mV).

dissociation of the drug, show a weaker ST-segment elevation than class IC drugs[22,24,25] (Figure 28-5B and C). Ajmaline (1 mg/kg, in 5 min, iv) has been frequently used and is reported to be safer with malignant ventricular arrhythmias in only 1.3% of the patients tested.[27] Wolpert *et al.* reported that ajmaline induced or enhanced Type 1 ST-segment elevation more frequently than flecainide, and that this was due to greater inhibition of I_{to} by flecainide.[28] Disopyramide (2 mg/kg in 10 min, iv) and procainamide (10 mg/kg, in 10 min, iv) show weaker accentuation of the ST-segment elevation due to their smaller effect on fast I_{Na} and mild to moderate action to block I_{to} (Figure 28-5C).[22,24,25] Class IB drugs (mexiletine, lidocaine, etc.) dissociate from the sodium channel rapidly and therefore have little or no effect on fast I_{Na} at moderate and slow heart rates, and thus are unable

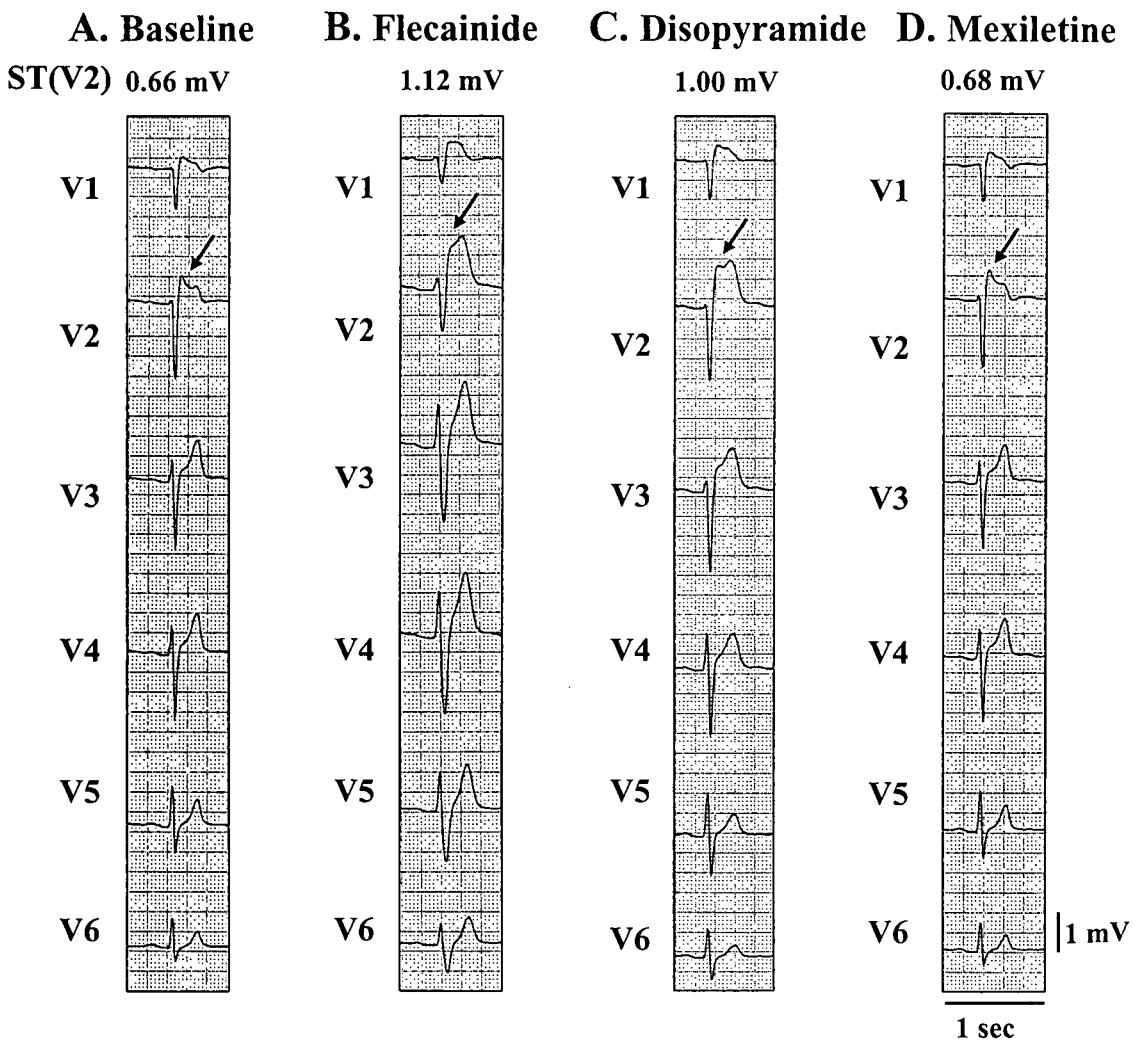

FIGURE 28-5. Effects of different sodium channel blockers on ST-segment elevation in a patient with Brugada syndrome. Six precordial lead electrocardiograms at baseline condition (A), after 100 mg flecainide injection (class IC drug) (B), after 100 mg disopyramide injection (class IA drug) (C), and after 125 mg mexiletine injection (class IB drug) are shown. At baseline conditions (A, arrow), Type 2 saddleback ST-segment elevation was seen in lead V2 (0.66 mV). Flecainide more remarkablly accentuated the ST-segment elevation (1.12 mV) than disopyramide (1.00 mV) (B and C, arrows), while mexiletine had no effect on the ST-segment elevation (0.68 mV) (D, arrow).

TABLE 28–2. Drugs used to unmask the Brugada syndrome.

Flecainide	2 mg/kg/10 min, iv (400 mg, po)
Pilsicainide	1 mg/kg/10 min, iv
Ajmaline	1 mg/kg/5 min, iv
Disopyramide	2mg/kg in 10 min, iv
Procainamide	10 mg/kg/10 min, iv

to cause ST-segment elevation[24] (Figure 28–5D). The recommended dosage of each sodium channel blocker is listed in Table 28–2.[29]

Practice of Testing with Sodium Channel Blockers

The definition of a positive provocative test is a development of the diagnostic Type 1 Brugada ECG (an increase in the absolute J wave amplitude of >0.2 mV with or without right bundle branch block in at least one of the V1–V3 leads) in the case of a Type 2, Type 3, or negative ECG at baseline. The test is considered positive upon an increase in the ST-segment elevation by >0.2 mV. The test does *not* add to the diagnostic value in patients with spontaneous and constant Type 1 Brugada ECG. The test should be monitored with a continuous 12-lead electrocardiographic recording (a speed of 10 mm/sec can be used to monitor throughout the test period, interposed with recordings at 25 or 50 mm/sec), and cardiopulmonary resuscitation facilities and isoproterenol infusion should be at hand. The endpoint of the test is when (1) the diagnostic Type 1 Brugada ECG develops, (2) the ST segment in Type 2 ECG increases by ≥0.2 mV, (3) ventricular or other arrhythmias develop, or (4) the QRS widens to ≥130% of baseline. Particular caution should be exercised in patients with a preexisting atrial and/or ventricular conduction disturbance (e.g., suspected cases of progressive cardiac conduction defect) or in the presence of wide QRS, wide P waves, or prolonged PR intervals (infranodal conduction disease) so as to avoid the risk of precipitating complete AV block.

Catecholaminergic Polymorphic Ventricular Tachycardia

Unlike LQTS and BrS in which the cardinal feature is often evident on the resting 12-lead ECG, this diagnostic test is *always* normal in CPVT. Phenotypically, CPVT mimics LQTS, particularly LQT1, with exercise-induced syncope, seizures, or sudden death, but in the setting of a structurally normal heart *and* a normal 12-lead ECG.[30,31] Approximately two-thirds of CPVT stems from mutations in the *RyR2*-encoded ryanodine receptor/calcium release channel (CPVT1). One possible clue for CPVT1 may be the presence of marked bradycardia.[32] However, the hallmark signature of CPVT is exercise-induced or catecholamine-induced bidirectional ventricular tachycardia.[33] Presently, it is not clear whether catecholamine provocation testing is additive to standard exercise stress testing or whether isoproterenol (more commonly used for CPVT) is superior to epinephrine.

Practically speaking, when faced with a patient presenting with exercise-induced syncope or exercise-induced aborted cardiac arrest and a normal ECG (QTc = 430 msec), the differential diagnosis includes both concealed LQT1 and CPVT. As such, we advocate using the epinephrine QT stress test (either the previously discussed Mayo or Shimizu protocols). Remember that significant epinephrine-induced ventricular ectopy is extremely uncommon in LQTS and occasional premature ventricular contractions (PVCs) and even couplets are not informative. If there is paradoxic QT lengthening, then concealed LQT1 is the presumptive clinical diagnosis. On the other hand, if there is epinephrine-induced bidirectional ventricular tachycardia, then CPVT is likely. Suspicion for CPVT should be raised and CPVT-directed genetic testing initiated for lesser degrees of epinephrine-induced ventricular ectopy such as epinephrine-induced nonsustained ventricular tachycardia, TdP in the absence of paradoxic QT lengthening, and possibly even PVCs in bigeminy during epinephrine infusion. One caveat to remember is that bidirectional ventricular tachycardia can also be seen in *KCNJ2*-mediated Andersen–Tawil syndrome.[34]

Acknowledgments. Dr. W. Shimizu was supported by the Uehara Memorial Foundation, Japan Research Foundation for Clinical Pharmacology, Ministry of Education, Culture, Sports, Science and Technology Leading Project for Biosimulation,

and health sciences research grants (H18-Research on Human Genome- 002) from the Ministry of Health, Labour and Welfare, Japan. Dr. Ackerman's research program was supported by the National Institutes of Health (HD42569), the American Heart Association (Established Investigator Award), the Doris Duke Charitable Foundation (Clinical Scientist Development Award), the CJ Foundation for SIDS, and the Dr. Scholl Foundation.

References

1. Schwartz PJ, Periti M, Malliani A. The long QT syndrome. *Am Heart J* 1975;89:378-390.
2. Schwartz PJ, Moss AJ, Vincent GM, Crampton RS. Diagnostic criteria for the long QT syndrome: An update. *Circulation* 1993;88:782-784.
3. Moss AJ, Schwartz PJ, Crampton RS, Locati E, Carleen E. The long QT syndrome: A prospective international study. *Circulation* 1985;71:17-21.
4. Shimizu W. The long QT syndrome: Therapeutic implications of a genetic diagnosis. *Cardiovasc Res* 2005;67:347-356.
5. Priori SG, Napolitano C, Schwartz PJ, Grillo M, Bloise R, Ronchetti E, Moncalvo C, Tulipani C, Veia A, Bottelli G, Nastoli J. Association of long QT syndrome loci and cardiac events among patients treated with beta-blockers. *JAMA* 2004;292: 1341-1344.
6. Vincent GM, Timothy KW, Leppert M, Keating M. The spectrum of symptoms and QT intervals in carriers of the gene for the long-QT syndrome. *N Engl J Med* 1992;327:846-852.
7. Priori SG, Napolitano C, Schwartz PJ. Low penetrance in the long-QT syndrome. Clinical impact. *Circulation* 1999;99:529-533.
8. Swan H, Saarinen K, Kontula K, Toivonen L, Viitasalo M. Evaluation of QT interval duration and dispersion and proposed clinical criteria in diagnosis of long QT syndrome in patients with a genetically uniform type of LQT1. *J Am Coll Cardiol* 1998;32:486-491.
9. Priori SG, Schwartz PJ, Napolitano C, Bloise R, Ronchetti E, Grillo M, Vicentini A, Spazzolini C, Nastoli J, Bottelli G, Folli R, Cappelletti D. Risk stratification in the long-QT syndrome. *N Engl J Med* 2003;348:1866-1874.
10. Schechter E, Freeman CC, Lazzara R. Afterdepolarizations as a mechanism for the long QT syndrome: Electrophysiologic studies of a case. *J Am Coll Cardiol* 1984;3:1556-1561.
11. Viskin S, Rosso R, Rogowski O, Belhassen B, Levitas A, Wagshal A, Katz A, Fourey D, Zeltser D, Oliva A, Pollevick GD, Antzelevitch C, Rozovski U. Provocation of sudden heart rate oscillation with adenosine exposes abnormal QT responses in patients with long QT syndrome: A bedside test for diagnosing long QT syndrome. *Eur Heart J* 2006;27: 469-475.
12. Ackerman MJ, Khositseth A, Tester DJ, Hejlik JB, Shen WK, Porter CB. Epinephrine-induced QT interval prolongation: A gene-specific paradoxical response in congenital long QT syndrome. *Mayo Clin Proc* 2002;77:413-421.
13. Noda T, Takaki H, Kurita T, Suyama K, Nagaya N, Taguchi A, Aihara N, Kamakura S, Sunagawa K, Nakamura K, Ohe T, Horie M, Napolitano C, Towbin JA, Priori SG, Shimizu W. Gene-specific response of dynamic ventricular repolarization to sympathetic stimulation in LQT1, LQT2 and LQT3 forms of congenital long QT syndrome. *Eur Heart J* 2002;23:975-983.
14. Vyas H, Hejlik J, Ackerman MJ. Epinephrine QT stress testing in the evaluation of congenital long-QT syndrome: Diagnostic accuracy of the paradoxical QT response. *Circulation* 2006;113: 1385-1392.
15. Khositseth A, Hejlik J, Shen WK, Ackerman MJ. Epinephrine-induced T-wave notching in congenital long QT syndrome. *Heart Rhythm* 2005;2: 141-146.
16. Shimizu W, Antzelevitch C. Differential response to beta-adrenergic agonists and antagonists in LQT1, LQT2 and LQT3 models of the long QT syndrome. *J Am Coll Cardiol* 2000;35:778-786.
17. Shimizu W, Noda T, Takaki H, Kurita T, Nagaya N, Satomi K, Suyama K, Aihara N, Kamakura S, Echigo S, Nakamura K, Sunagawa K, Ohe T, Towbin JA, Napolitano C, Priori SG. Epinephrine unmasks latent mutation carriers with LQT1 form of congenital long QT syndrome. *J Am Coll Cardiol* 2003;41:633-642.
18. Shimizu W, Noda T, Takaki H, Nagaya N, Satomi K, Kurita T, Suyama K, Aihara N, Sunagawa K, Echigo S, Miyamoto Y, Yoshimasa Y, Nakamura K, Ohe T, Towbin JA, Priori SG, Kamakura S. Diagnostic value of epinephrine test for genotyping LQT1, LQT2 and LQT3 forms of congenital long QT syndrome. *Heart Rhythm* 2004;1:276-283.
19. Shimizu W, Tanabe Y, Aiba T, Inagaki M, Kurita T, Suyama K, Nagaya N, Taguchi A, Aihara N, Sunagawa K, Nakamura K, Ohe T, Towbin JA, Priori SG, Kamakura S. Differential effects of β-blockade on dispersion of repolarization in absence and presence of sympathetic stimulation between

LQT1 and LQT2 forms of congenital long QT syndrome. *J Am Coll Cardiol* 2002;39:1984–1991.
20. 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.
21. Matsuo K, Shimizu W, Kurita T, Inagaki M, Aihara N, Kamakura S. Dynamic changes of 12-lead electrocardiograms in a patient with Brugada syndrome. *J Cardiovasc Electrophysiol* 1998;9:508–512.
22. Miyazaki T, Mitamura H, Miyoshi S, Soejima K, Aizawa Y, Ogawa S. Autonomic and antiarrhythmic drug modulation of ST segment elevation in patients with Brugada syndrome. *J Am Coll Cardiol* 1996;27:1061–1070.
23. 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.
24. Shimizu W, Antzelevitch C, Suyama K, Kurita T, Taguchi A, Aihara N, Takaki H, Sunagawa K, Kamakura S. 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.
25. Brugada R, Brugada J, Antzelevitch C, Kirsch GE, Potenza D, Towbin JA, Brugada P. 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.
26. Morita H, Morita ST, Nagase S, Banba K, Nishii N, Tani Y, Watanabe A, Nakamura K, Kusano KF, Emori T, Matsubara H, Hina K, Kita T, Ohe T. Ventricular arrhythmia induced by sodium channel blocker in patients with Brugada syndrome. *J Am Coll Cardiol* 2003;42:1624–1631.
27. Rolf S, Bruns HJ, Wichter T, Kirchhof P, Ribbing M, Wasmer K, Paul M, Breithardt G, Haverkamp W, Eckardt L. The ajmaline challenge in Brugada syndrome: Diagnostic impact, safety, and recommended protocol. *Eur Heart J* 2003;24:1104–1112.
28. Wolpert C, Echternach C, Veltmann C, Antzelevitch C, Thomas GP, Spehl S, Streitner F, Kuschyk J, Schimpf R, Haase KK, Borggrefe M. Intravenous drug challenge using flecainide and ajmaline in patients with Brugada syndrome. *Heart Rhythm* 2005;2:254–260.
29. Antzelevitch C, Brugada P, Borggrefe M, Brugada J, Brugada R, Corrado D, Gussak I, Lemarec H, Nademanee K, Perez Riera AR, Shimizu W, Schulze-Bahr E, Tan H, Wilde A. Brugada syndrome. Report of the Second Consensus Conference. Endorsed by the Heart Rhythm Society and the European Heart Rhythm Association. *Circulation* 2005;111:659–670.
30. Leenhardt A, Lucet V, Denjoy I, Grau F, Ngoc DD, Coumel P. Catecholaminergic polymorphic ventricular tachycardia in children. A 7-year follow-up of 21 patients. *Circulation* 1995;91:1512–1519.
31. Priori SG, Napolitano C, Memmi M, Colombi B, Drago F, Gasparini M, DeSimone L, Coltorti F, Bloise R, Keegan R, Cruz Filho FE, Vignati G, Benatar A, DeLogu A. Clinical and molecular characterization of patients with catecholaminergic polymorphic ventricular tachycardia. *Circulation* 2002;106:69–74.
32. Postma AV, Denjoy I, Kamblock J, Alders M, Lupoglazoff JM, Vaksmann G, Dubosq-Bidot L, Sebillon P, Mannens MM, Guicheney P, Wilde AA. Catecholaminergic polymorphic ventricular tachycardia: RYR2 mutations, bradycardia, and follow up of the patients. *J Med Genet* 2005;42:863–870.
33. Cerrone M, Colombi B, Santoro M, di Barletta MR, Scelsi M, Villani L, Napolitano C, Priori SG. Bidirectional ventricular tachycardia and fibrillation elicited in a knock-in mouse model carrier of a mutation in the cardiac ryanodine receptor. *Circ Res* 2005;96:1031–1032.
34. Tester DJ, Arya P, Will M, Haglund CM, Farley AL, Makielski JC, Ackerman MJ. Genotypic heterogeneity and phenotypic mimicry among unrelated patients referred for catecholaminergic polymorphic ventricular tachycardia genetic testing. *Heart Rhythm* 2006;3:800–805.

47
Acquired Form of Brugada Syndrome

Wataru Shimizu

Brugada Syndome

Brugada and Brugada reported in 1992 eight patients with a history of aborted sudden cardiac death due to ventricular fibrillation (VF) and a characteristic electrocardiographic pattern, consisting of right bundle branch block (RBBB) and ST-segment elevation in the right precordial electrocardiogram (ECG) (V1–V3) as a distinct clinical entity.[1-8] The presence of RBBB was thereafter revealed to be not necessary for the diagnosis of Brugada syndrome, although mild to moderate widening of the QRS duration is often observed.[5] Two specific types of ST-segment elevation, coved and saddleback, are observed in this syndrome. The ST-segment elevation is often accentuated and the coved type ST-segment elevation is more frequently recognized just before and after episodes of VF.[9,10] The Brugada Consensus Report in 2002 suggested three patterns of ST-segment elevation in the right precordial ECG.[5] Type 1 is characterized by a coved type ST-segment elevation displaying J wave amplitude or ST-segment elevation of ≥0.2 mV followed by a negative T wave (Figure 47–1A). Type 2 has a saddleback configuration, which has a high take-off ST-segment elevation (≥0.2 mV) followed by a gradually descending ST-segment elevation (remaining ≥0.1 mV above the baseline) and a positive or biphasic T wave (Figure 47–1B). Type 3 has an ST-segment elevation of <0.1 mV of the saddleback, coved type, or both. The second Consensus Report published in 2005, however, emphasized that Type 1 coved ST-segment elevation is required to diagnose Brugada syndrome,[7] because the Type 1 ECG is reported to relate to a higher incidence of VF and sudden cardiac death.[6] Type 2 and Type 3 ST-segment elevation are not diagnostic for the Brugada syndrome. The recordings of V1 and V2 leads at higher (third and second) intercostal spaces increase the sensitivity and the specificity of the ECG diagnosis for detecting the Brugada phenotype (Figure 47–1C),[7,11] and their diagnostic and prognostic values have recently been reported.[12]

Molecular Aspects

In 1998, Chen and co-workers identified the first mutation linked to Brugada syndrome in *SCN5A*, the gene encoding the α subunit of the sodium channel.[13] Antzelevitch and co-workers have recently reported that three probands associated with a Brugada like ST-segment elevation and a short QT interval were linked to mutations in *CACNA1C* (A39V and G490R) or *CACNB2* (S481L), the gene encoding the α1 or β2b subunit of the L-type calcium channel ($I_{Ca\text{-}L}$), respectively.[14] However, approximately tow-thirds of Brugada patients have not been yet genotyped, suggesting the presence of genetic heterogeneity.[8] Other candidate genes for the Brugada phenotype include the genes encoding transient outward current (I_{to}), and delayed rectifier potassium current (I_K), or genes that code for adrenergic receptors, cholinergic receptors, ion-channel-interacting protein, promoters, transcriptional factors, neurotransmitters, or transporters.

Functional analysis employing expression systems was reported in approximately two dozen

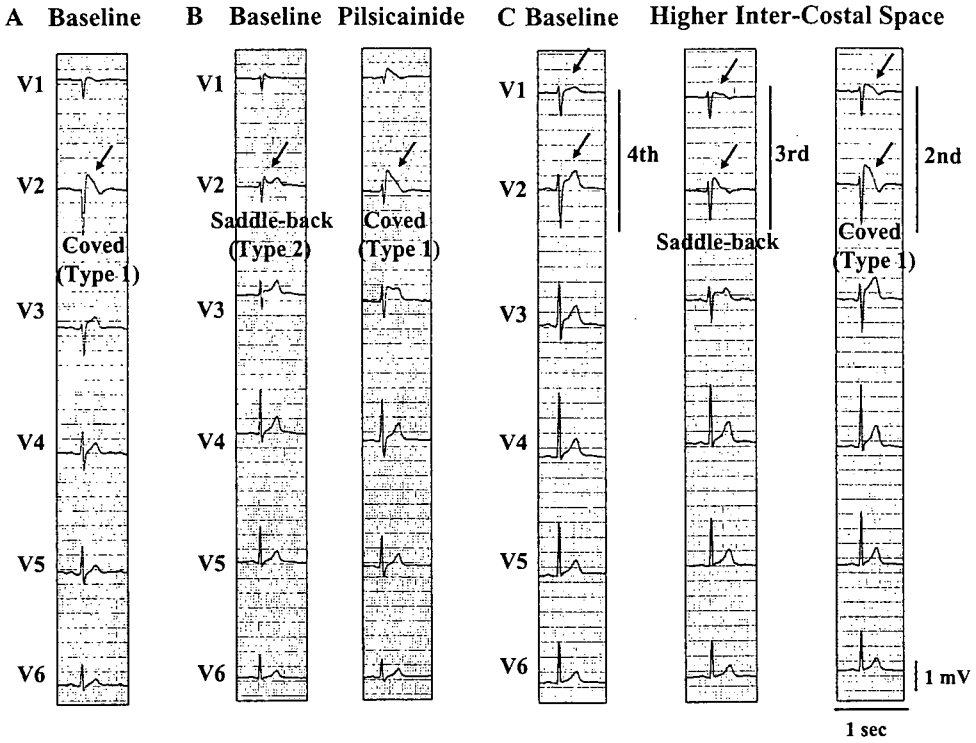

FIGURE 47–1. Type 1 coved ST-segment elevation spontaneously or unmasked by pilsicainide or higher intercostal space recordings of V1 and V2 leads. (A) Spontaneously Type 1 coved ST-segment elevation. (B) Although Type 2 saddleback ST-segment elevation was seen in a V2 lead under baseline conditions, pilsicainide, a class IC drug, unmasked Type 1 coved ST-segment elevation in a V2 lead (arrow). (C) Although no ST-segment elevation was observed at standard (fourth intercostal space) V1 and V2 leads under baseline conditions (arrows), a Type 1 coved ST-segment elevation was recorded at higher (second intercostal space) V1 and V2 leads (arrows).

of the mutations in *SCN5A*, and demonstrated that all of the mutations resulted in "loss of function" of I_{Na} by several mechanisms.[13,15–17] These functional effects include (1) failure of the sodium channel to express, (2) a shift in the voltage and time dependence of I_{Na} activation, inactivation, or reactivation, (3) entry of the sodium channel into an intermediate state of inactivation from which it recovers more slowly, (4) accelerated inactivation of the sodium channel, or (5) trafficking defect.

Cellular Mechanism of Brugada Phenotype

An I_{to}-mediated phase 1 notch of the action potential (AP) has been reported to be greater in the epicardial cells than in the endocardial cells in many species, including humans, by experimental studies.[18] Since the maintenance of the AP dome is determined by the fine balance of currents active at the end of phase 1 of the AP (principally I_{to} and $I_{Ca\text{-}L}$), any agents that cause a net outward shift at the end of phase 1 can increase the magnitude of the AP notch, leading to loss of the AP dome (all-or-none repolarization) in the epicardium, but not in the endocardium, contributing to a significant voltage gradient across the ventricular wall during ventricular activation.[18] The heterogeneous loss of the AP dome in the epicardium was shown to produce premature beats via a mechanism of phase 2 reentry in experimental studies using isolated sheets of canine right ventricle.[19] The Brugada syndrome seems to be a clinical counterpart of the mechanism of all-or-none repolarization in the epicardial cells and phase 2 reentry-induced premature beat between the adjacent epicardial cells.

An experimental model of the Brugada syndrome employing arterially perfused canine right

ventricular (RV) wedge preparations provided direct experimental evidence for the cellular mechanism of ST-segment elevation.[20] The I_{to}-mediated AP notch and the loss of the AP dome in the epicardial cells, but not in the endocardial cells, of the right ventricle gives rise to a transmural voltage gradient, producing ST-segment elevation in the ECG (Figure 47–2).[8] In the setting of coved type ST-segment elevation, heterogeneous loss of the AP dome (the coexistence of loss of dome regions and restored dome regions) in the epicardium creates a marked epicardial dispersion of repolarization, giving rise to premature beats due to phase 2 reentry, which sometimes precipitates nonsustained polymorphic ventricular tachycardia (VT) or VF (Figure 47–2).[8]

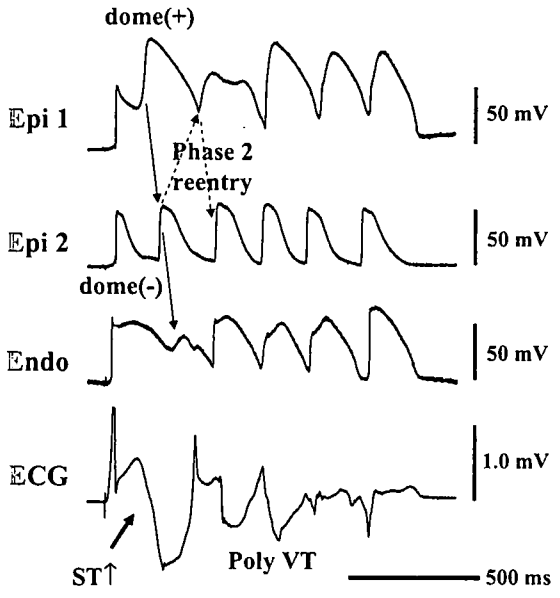

FIGURE 47–2. Coved ST-segment elevation and phase 2 reentry-induced nonsustained polymorphic ventricular tachycardia (poly VT) in a Brugada model employing an arterially perfused canine right ventricular wedge preparation. Transmembrane action potentials simultaneously recorded from two epicardial (Epi) sites and one endocardial (Endo) site together with a transmural electrocardiogram (ECG) (BCL 2000 msec). Combined administration of terfenadine (5 μM) and pilsicainide (5 μM) causes heterogeneous loss of the action potential dome in the epicardium (restored dome in epicardial site 1, loss of dome in epicardial site 2), giving rise to a coved type Brugada ECG. Electrotonic propagation from the site where the dome is restored (Epi 1) to the site where it is lost (Epi 2) results in development of phase 2 reentry-induced premature beats, triggering poly VT.

Our recently developed high-resolution optical mapping system, which allows us to record transmembrane APs from 256 sites simultaneously, suggested that a steep repolarization gradient between a loss of dome region and a restored dome region in the epicardium is essential to produce phase 2 reentry-induced premature beats, and that mild to moderate conduction delay is required to degenerate the reentrant pathway into VF.[8,21]

Acquired Form of Brugada Syndrome

The ST-segment elevation is well known to be dynamic day-to-day even in the same patient with Brugada syndrome, and to be modulated by several drugs (mainly antiarrhythmic drugs) and autonomic agents.[22] Class IC antiarrhythmic drugs, which are used as a diagnostic tool in latent Brugada syndrome, amplify or unmask the ST-segment elevation most effectively as a result of their strong effect of blocking fast I_{Na}.[23,24] Several drugs and conditions other than IC drugs are reported to induce transient ST-segment elevation like that in Brugada syndrome. Based on the molecular and cellular aspects in Brugada syndrome mentioned above, any interventions that increase outward currents (e.g., I_{to}, adenosine triphosphate-sensitive potassium current [$I_{K\text{-}ATP}$], slow and fast activating components of I_K [I_{Ks}, I_{Kr}]) or decrease inward currents (e.g., $I_{Ca\text{-}L}$, fast I_{Na}) at the end of phase 1 of the AP can accentuate or unmask ST-segment elevation, similar to that found in Brugada syndrome. This is described as an "acquired" form of Brugada syndrome similar to the "acquired" form of long QT syndrome (LQTS) (Table 47–1).

Antiarrhythmic Drugs

Class IC sodium channel blockers (flecainide, propafenone, pilsicainide) produce the most pronounced ST-segment elevation secondary to strong use-dependent blocking of fast I_{Na} due to their slow dissociation from the sodium channels.[23–28] Pilsicainide, a pure class IC drug developed in Japan, is thought to more strongly induce ST-segment elevation than flecainide, which is widely used throughout the world and mildly blocks I_{to}.