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Review

Brugada Syndrome: 12 Years of Progression

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Brugada syndrome is increasingly being recognized in clinical medicine. What started as an electrocardiographic curiosity has become an important focus of attention for individuals working in the different disciplines related to sudden cardiac death, from basic scientists to clinical cardiac electrophysiologists. In just 12 years, since the description of the disease, clinically relevant information is continuously being provided to physicians to help protect the individuals with Brugada syndrome to the best of our ability. And this information has been gathered thanks to the effort of hundreds of basic scientists, physicians and patients who continue to give their time, effort and data to help understand how the electrocardiographic pattern may cause sudden cardiac death. There are still many unanswered questions, both at the clinical and basic field. However, with the further collection of data, the longer follow-up and the continued interest from the basic science world we will have the necessary tools to the successful unraveling of the disease.

Key words: Brugada syndrome, sudden death, genetics

Since its initial description in the early nineties [1], Brugada syndrome has attracted progressively more attention in the cardiology community. There are several reasons for it becoming such a focal point of attention. First, the disease takes the lives, in many instances as a first event, of previously healthy individuals in their forties, during their most productive years [2]. This creates great anxiety among family members and a desperate need to identify other mutation carriers among the offspring of affected individuals, usually very young children. Second, once thought to be very rare, the Brugada syndrome is now recognized worldwide and has a relatively high prevalence in certain parts of the world, particularly the Southeast Asia. Third, the identification of the disease coincided with a burst of activity in the molecular biology and cardiology fields. Brugada syndrome has benefited greatly from the knowledge and experience gained in the field of molecular cardiology and genetics of other arrhythmogenic diseases. Fourth, recent years have witnessed the bridging of clinical and basic sciences related to our understanding of the Brugada syndrome. The interactive exchange between disciplines has assisted physicians and scientists alike in formulation

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of better approaches to the diagnosis and treatment of the disease. Finally, despite the great strides of the past decade, several challenges and questions still remain. The ECG pattern of the Brugada Syndrome may be concealed and even transiently normalize (Fig. 1). It may also appear under the influence of some external factors like tryciclic antidepressant overdose, fever, cocaine, anesthetics, *etc.* [3]. It is not entirely clear whether these patients are at higher or lower risk of sudden death. The biggest challenge by far is the limited therapeutic options available for the disease. Brugada syndrome is a very malignant disease with a high rate of recurrence of life-threatening events. The only proven effective treatment at this point is the implantation of a defibrillator, which is largely unaffordable where the disease is most prevalent. An alternative approach to therapy is therefore needed for these individuals. All of these factors continue to drive both clinical and basic research at medical centers worldwide.

Basic research into the mechanisms underlying the Brugada syndrome is in its infancy and the next 10 years will probably provide still better understanding of this lethal disease. What started as an electrocardiographic curiosity has become a great challenge for electrophysiologists, cardiologists, biophysicists, geneticists and molecular biologists.

Ionic and Cellular Mechanisms

The past several decades have provided us with important insights into the electrical function of the ventricular myocardium. What was once thought to be a homogeneous tissue consisting of muscular and conducting tissue, is now recognized as being a heterogeneous milieu with multiple cellular subtypes with different functional and electrophysiological properties [4]. These electrophysiological distinctions are due to variations in the expression of ionic currents, especially between epicardium and endocardium. These differences contribute to the development of ST segment elevation and the substrate for reentrant arrhythmias. Experiments involving the arterially perfused right ventricular wedge preparation have shown that the epicardial action potential notch is responsible for the inscription of the electrocardiographic J wave and that accentuation of the notch leads to amplification of the J wave, resulting in an apparent elevation of the ST segment [5]. This has been shown in pathophysiological states like hypothermia, where an increase in the action potential notch in epicardium but not endocardium, causes an elevation of the J point and ST segment in the electrocardiogram. If the epicardial action potential repolarizes before that of the endocardium, the T wave will remain positive and the electrocardiogram will show a saddle-back type of ST segment elevation. Further accentuation of the pathophysiological state will

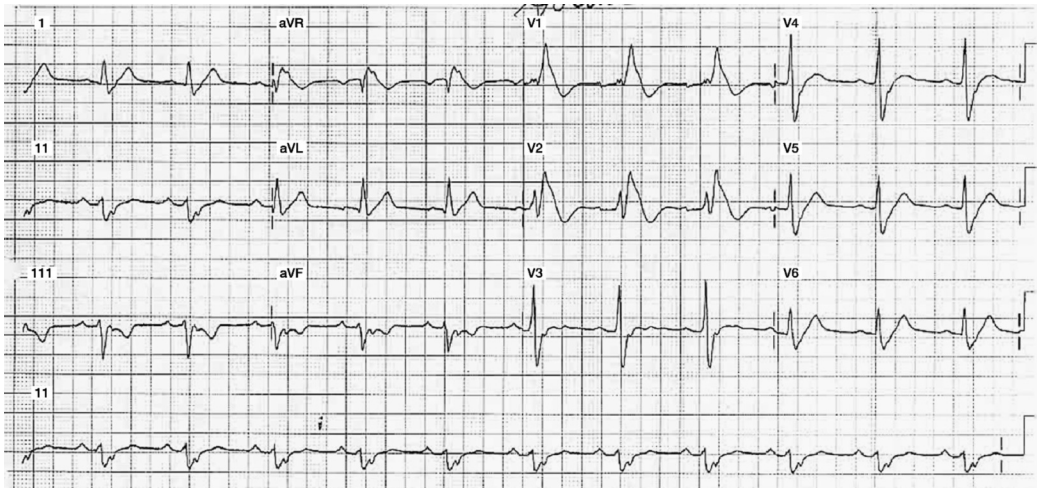

Fig. 1 Typical electrocardiographic pattern of ST segment elevation in right ventricular precordial leads consistent with the Brugada syndrome.

accentuate the notch and prolong the epicardial action potential so that it repolarizes after the endocardial response, thus leading to inversion of the T wave. The result is an electrocardiogram with a coved ST segment elevation and a negative T wave, but no clear arrhythmogenic substrate. Progressive accentuation of the notch will eventually lead to loss of the action potential dome and marked abbreviation of the epicardial response at some sites [6] thus creating an epicardial as well as transmural dispersion of repolarization and the substrate for reentrant arrhythmias [7] (Fig. 2). Very few papers have addressed the epicardial recording of action potentials for obvious technical reasons. Recordings from the conus branch have indicated that there is the recording of late potentials in epicardium but not endocardium [8].

Experimental models of the Brugada syndrome created by exposing right ventricular wedge preparations to a variety of pharmacological agents have highlighted the importance of Ito. The high expression of Ito during phase 1 of the action potential plays a pivotal role in the electrocardiographic pattern of the Brugada syndrome. It is the balance of currents active during phase 1 that determines the degree of ST segment elevation. The use of quinidine, a class IA antiarrhythmic with action to block Ito, among other currents, has been shown to be capable of restoring the action potential dome in epicardium, thus normalizing the ST segment elevation [6]. It is certainly a finding which could have clinical and therapeutic relevance. There is a group that advocates the use of this antiarrhythmic to treat Brugada syndrome [9] and there has been a case report in the literature of decreased ST elevation with the use of quinidine [10].

Sodium channel blockers also increase the notch of the epicardial action potential and thus give rise to an ST segment elevation in the wedge preparation [6]. This has also proved useful in clinical practice as a diagnostic tool to unmask the electrocardiographic pattern in individuals suspected of having the Brugada syndrome. Sodium blockers like ajmaline, procainamide, flecainide and pilsicainide are now being used to identify the individuals at risk [11]. Rare but potentially life-threatening arrhythmias have been described with the use of the sodium

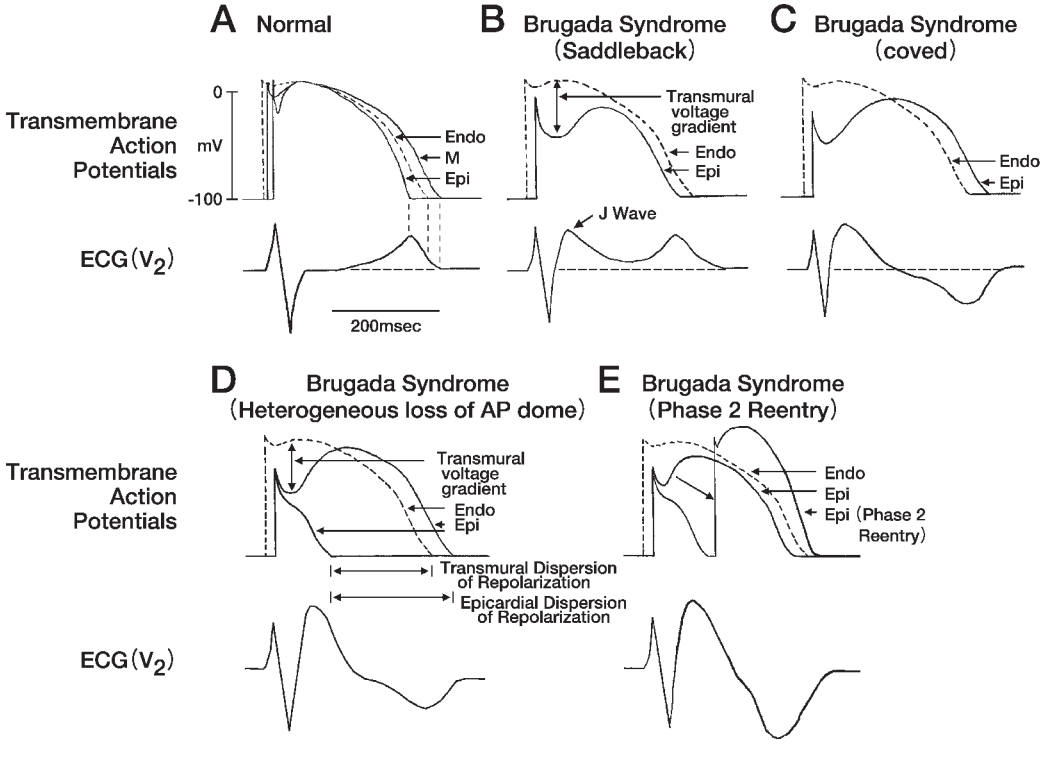

Fig. 2 Schematic representation of right ventricular epicardial action potential changes proposed to underlie the electrocardiographic manifestation of early repolarization and Brugada syndrome (from [37] with permission).

blockers to test for possible Brugada syndrome, indicating the need of performing this test under close monitoring and resuscitation equipment [12].

Two intriguing questions have arisen in recent years. One is why is this electrocardiographic pattern only present in the right precordial leads, and the second is why the Brugada phenotype is so much more prevalent in males *vs.* females of South East Asian origin. Answers to both questions derive from recent studies conducted in the wedge preparation. In brief, the reasons have to do with the fact that Ito is much more prominent in males *vs.* females [13] and is much greater in the right *vs.* left ventricles of the heart [14].

Genetics

A definitive link between the sodium currents and Brugada syndrome has been provided by research in genetics. The first gene responsible for the disease was identified in 1998 by Chen and coworkers [15]. This gene, the α-subunit of the cardiac sodium channel gene, SCN5A, is responsible for the phase 0 of the cardiac action potential. The identification of mutations in SCN5A causing the disease and the decrease in availability of sodium ions, suggest that a shift in the ionic balance in favor of Ito during phase 1 of the action potential is the determinant of the disease [7]. To date, this is the only gene linked to Brugada syndrome. SCN5A has been identified in approximately 25% of the patients with Brugada syndrome, indicating that there is at least another gene responsible for the disease. In 2002, a second locus, on chromosome 3 was identified, although the gene responsible has not been identified as yet [16]. Close to 60 different mutations in SCN5A have been reported to date and approximately one third of them have been biophysically characterized. The common denominator in the analysis of the mutations is the decrease in Na current availability by 3 principal mechanisms: lack of expression of the mutant channel, a shift in the voltage dependence of activation, inactivation and reactivation or acceleration of inactivation of the channel [17]. These are at this point considered the main pathophysiological mechanisms causing Brugada syndrome. In the case of T1620 M mutation, the alteration in the ionic currents is exaggerated at higher temperatures [18]. This too may have some clinical correlation as there have been several cases of ventricular fibrillation in patients with Brugada syndrome that develop during febrile states [19–21].

Brugada syndrome is usually a disease that affects individuals in their forties. However, it has also been described as causing sudden infant death syndrome (SIDS) [22]. In addition to Brugada syndrome, mutations of SCN5A can lead to a large spectrum of phenotypes, including long-QT syndrome (LQT3) [23], isolated progressive cardiac conduction defect [24], idiopathic ventricular fibrillation [15], and sudden unexplained nocturnal death syndrome (SUDS or SUNDS) [25]. These are all considered to be allelic diseases, caused by mutations in a same gene (Fig. 3).

Brugada syndrome could be considered a mirror image of LQT3. Biophysical data indicate that LQT3 mutations cause a delayed inactivation of the channel [23], which is exactly the opposite as in Brugada syndrome, where there is an accelerated inactivation [18]. The difference between the 2 diseases is however difficult to identify in some cases, and one family has been described manifesting the phenotype of both Brugada and long QT syndromes [26]. Likewise, the line between progressive conduction disease and Brugada syndrome is closer than ever after the publication of a paper with a family displaying both diseases [27]. Whether they represent variable phenotypic expression of the same disease is not clear. One thing appears to be true, all the affected family members in this family, with Brugada syndrome or conduction disease, have a mutation that has proven lethal to some of its members. This raises important issues regarding therapy, prevention and risk stratification.

Recent studies have shed some light on the distinctions or lack thereof between Brugada syndrome and Sudden Unexpected Death Syndrome (SUDS) in Southeast Asia. SUDS is very prevalent in Southeast Asia. In countries like Thailand, it is believed to affect up to 1% of the population, and it is the most common cause of death in young males, second only to car accidents [28]. The patients commonly die at night and the male to female ratio is on the order of 10:1. Electrocardiographically, the disease is identical to Brugada syndrome. It is also caused by mutations in SCN5A and biophysical data indicates a non-working SCN5A or accelerated inactivation [25]. These characteristics are similar to those of the Brugada syndrome, suggesting that they are the same disease. The identification of the same mutation in a family of European descent as in a family of Japanese descent provided a clear indication that the two are actually the same disease [29].

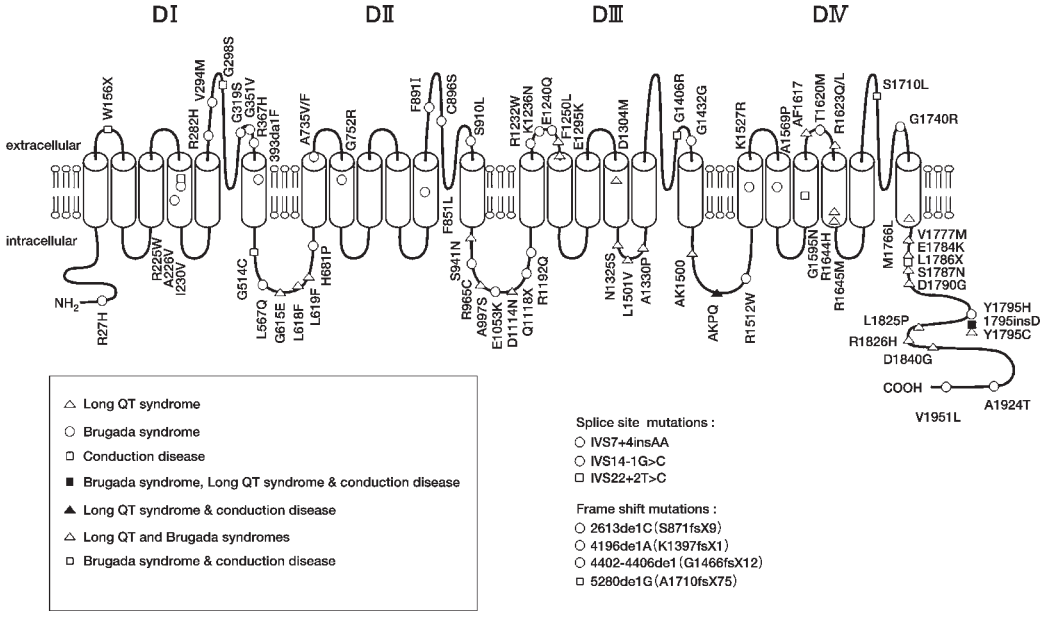

Fig. 3 Diagrammatic representation of the human cardiac sodium channel displaying locations of mutations associated with Long QT syndrome type 3, Brugada syndrome, isolated cardiac conduction disease, and overlap syndromes. I, domain I; II, domain II; III, domain III; IV, domain IV.

Clinical Characteristics

It is certainly a challenge to risk stratify patients with Brugada syndrome. There are many uncertainties that are gradually coming into better focus as patients and families are identified. Electrocardiographic criteria have been used to try to risk stratify patients, but not all research groups agree on the criteria to be applied. Some of the conclusions are as follows.

Symptomatic patients are at high risk for recurrence. There is a consensus that symptomatic patients with documented ventricular fibrillation have close to a 50% chance of having another event within 5 years. If the patient experienced syncope, the recurrence rate is 20% [30].

Asymptomatic individuals with normal ECG at baseline and abnormal ECG after sodium channel blockers have a relatively good prognosis. Individuals that have the mutation but require a sodium block challenge to develop the abnormal electrocardiographic pattern may have environmental or other genetic alterations that protect them. A note of caution is required in this analysis; since many of these are relatively young individuals, much younger than the symptomatic group, and how their disease will progress as they grow older is not known [30].

Individuals with an electrocardiographic pattern that normalizes are at the same risk as other patients with a persistent ECG abnormality. If the substrate for arrhythmias depends on the transmural voltage gradient, it would seem that patients would develop reentrant arrhythmias more often while there is ST segment elevation. It is of course possible that the ST segment elevation will appear just moments before the episode of ventricular fibrillation. More data and patients will be required to estimate the real value of transient versus persistent ST segment elevation.

Those with a coved type ECG are at higher risk than saddle back type. Actually, our group does not accept a diagnosis of Brugada syndrome without a coved type ECG either before or after sodium blocker drug challenge. Again, this may correspond to the severity of the defect that throws off the balance of currents during the early phases of the action potential, as previously discussed. Our current understanding of basic mechanisms is that the substrate for VT/VF is unlikely to be present when only a saddleback type of ST segment elevation is manifest, but more likely in the presence of a coved type. Consis-

tent with this hypothesis is the clinical observation that saddleback ST segment elevation usually progresses to a coved type before VT/VF is observed.

The use of potent sodium channel blockers to diagnose patients at risk for Brugada syndrome has raised some controversy. There is a wide variety of medications used to unmask the disease. False negative results have been reported with procainamide and flecainide [31]. False positive results have been reported with flecainide in patients with LQT3 [32]. The value of the antiarrhythmic challenge should come into better focus as more people are tested and genotyped for mutations.

The most controversial issue is the value of electrophysiological study as an indicator of prognosis. Studies from Priori [31], Shimizu [33] and Eckardt [34] have not found an association between inducibility and recurrence of events. Our data of close to 700 patients indicates that EP study inducibility is prognostic of risk. The use of electrophysiological data is probably not clinically necessary in the patient that has recovered from sudden cardiac death. There is not much room for argument that they require a defibrillator. Where the controversy arises is on how aggressive we need to be with asymptomatic patients. There is no doubt that asymptomatic patients are also at risk. Brugada syndrome generally affects individuals in their forties, despite the fact that the genetic predisposition is present since birth. What determines the likelihood of a patient becoming symptomatic is at present unknown, but the one thing that is certain is that all symptomatic patients had previously been asymptomatic for many years. Identifying which group will become symptomatic is a critically important preventative measure. Asymptomatic patients without a family history of sudden death have been found to have a benign course especially if they are non-inducible at electrophysiological study [35]. Our group has shown that patients with Brugada syndrome and no previous history of cardiac arrest have an 8% chance of having a documented ventricular fibrillation and/or sudden death in the following 2 years. Inducibility and previous history of syncope are markers of poor prognosis [36]. We therefore advocate the implantation of a defibrillator in asymptomatic inducible patients. The rest require close follow-up until evidence-based data provide further guidance for risk stratification.

Concluding Remarks

The past decade has witnessed the identification of a new clinical entity responsible for sudden death in the young and the evolution of a strategy to diagnose, risk stratify and treat patients with this syndrome. This has been possible thanks to the efforts of many centers around the world and to the collaboration of hundreds of physicians. This is still a very new disease, with a high social impact due to the fact that it involves death of relatively young individuals. Through research and continued collaboration among the basic and clinical groups involved, we look forward to advances that will enable us to better identify those at risk and provide the means to treat them more effectively, so as to reduce the burden of this disease on the affected families.

References

1. Brugada P and 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.
2. Brugada J, Brugada R and Brugada P: Right bundle-branch block and ST-segment elevation in leads V_1 through V_3. A marker for sudden death in patients without demonstrable structural heart disease. Circulation (1998) 97: 457–460.
3. Wilde AA, Antzelevitch C, Borggrefe M, Brugada J, Brugada R, Brugada P, Corrado D, Hauer RN, Kass RS, Nademanee K, Priori SG and Towbin JA: Proposed diagnostic criteria for the Brugada syndrome: Consensus Report. Eur Heart J (2002) 23: 1648–1654.
4. Antzelevitch C, Brugada P, Brugada J, Brugada R, Shimizu W, Gussak I and Perez Riera AR: Brugada Syndrome. A Decade of Progress. Circ Res (2002) 91: 1114–1118.
5. Antzelevitch C and Yan GX: Cellular and ionic mechanisms responsible for the Brugada syndrome. J Electrocardiol (2000) 33 Suppl: 33–39.
6. Yan GX and Antzelevitch C: Cellular basis for the Brugada Syndrome and other mechanisms of arrhythmogenesis associated with ST-segment elevation. Circulation (1999) 100: 1660–1666.
7. Antzelevitch C: The Brugada Syndrome: diagnostic criteria and cellular mechanisms. Eur Heart J (2001) 22: 356–363.
8. Nagase S, Kusano KF, Morita H, Fujimoto Y, Kakishita M, Nakamura K, Emori T, Matsubara H and Ohe T: Epicardial electrogram at the right ventricular outflow tract in patients with the Brugada syndrome: using epicardial lead. J Am Coll Cardiol (2002) 39: 1992–1995.
9. Belhassen B, Viskin S, Fish R, Glick A, Setbon I and Eldar M: Effects of electrophysiologic-guided therapy with Class IA antiarrhythmic drugs on the long-term outcome of patients with idiopathic ventricular fibrillation with or without the Brugada syndrome. J Cardiovasc Electrophysiol (1999) 10: 1301–1312.
10. Alings M, Dekker L, Sadee A and Wilde A: Quinidine induced electrocardiographic normalization in two patients with Brugada syndrome. Pacing Clin Electrophysiol (2001) 24: 1420–1422.
11. Brugada R, Brugada J, Antzelevitch C, Kirsch GE, Potenza D, Towbin JA and 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.
12. 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 and Ohe T: Ventricular arrhythmia induced by sodium channel blocker in patients with Brugada syndrome. J Am Coll Cardiol (2003) 42: 1624–1631.
13. Di Diego JM, Cordeiro JM, Goodrow RJ, Fish JM, Zygmunt AC, Perez GJ, Scornik FS and Antzelevitch C: Ionic and cellular basis for the predominance of the Brugada syndrome phenotype in males. Circulation (2002) 106: 2004–2011.
14. Di Diego JM, Sun ZQ and Antzelevitch C: I_{to} and action potential notch are smaller in left *vs*. right canine ventricular epicardium. Am J Physiol (1996) 271: H548-H561.
15. Chen Q, Kirsch GE, Zhang D, Brugada R, Brugada J, Brugada P, Potenza D, Moya A, Borggrefe M, Breithardt G, Ortiz-Lopez R, Wang Z, Antzelevitch C, O'Brien RE, Schultze-Bahr E, Keating MT, Towbin JA and Wang Q: Genetic basis and molecular mechanism for idiopathic ventricular fibrillation. Nature (1998) 392: 293–296.
16. Weiss R, Barmada MM, Nguyen T, Seibel JS, Cavlovich D, Kornblit CA, Angelilli A, Villanueva F, McNamara DM and London B: Clinical and molecular heterogeneity in the Brugada syndrome. A novel gene locus on chromosome 3. Circulation (2002) 105: 707–713.
17. Brugada R and Roberts R: Brugada syndrome: why are there multiple answers to a simple question? Circulation (2001) 104: 3017–3019.
18. Dumaine R, Towbin JA, Brugada P, Vatta M, Nesterenko DV, Nesterenko VV, Brugada J, Brugada R and Antzelevitch C: Ionic mechanisms responsible for the electrocardiographic phenotype of the Brugada syndrome are temperature dependent. Circ Res (1999) 85: 803–809.
19. Porres JM, Brugada J, Urbistondo V, Garcia F, Reviejo K and Marco P: Fever unmasking the Brugada syndrome. Pacing Clin Electrophysiol (2002) 25: 1646–1648.
20. Saura D, Garcia-Alberola A, Carrillo P, Pascual D, Martinez-Sanchez J and Valdes M: Brugada-like electrocardiographic pattern induced by fever. Pacing Clin Electrophysiol (2002) 25: 856–859.
21. Antzelevitch C and Brugada R: Fever and Brugada Syndrome. PACE (2002) 25: 1537–1539.
22. Priori SG, Napolitano C, Giordano U, Collisani G and Memmi M: Brugada syndrome and sudden cardiac death in children. Lancet (2000) 355: 808–809.
23. Roden DM, Lazzara R, Rosen M, Schwartz PJ, Towbin JA, Vincent GM, The SADS Foundation Task Force on LQTS, Antzelevitch C, Brown AM, Colatsky TJ, Crampton RS, Kass RS, Moss AJ, Sanguinetti MC and Zipes DP: Multiple mechanisms in the long-QT syndrome: Current knowledge, gaps, and future directions. Circulation (1996) 94: 1996–2012.
24. Schott JJ, Alshinawi C, Kyndt F, Probst V, Hoorntje TM, Hulsbeek M, Wilde AA, Escande D, Mannens MM and Le Marec H: Cardiac conduction defects associate with mutations in SCN5A. Nat Genet (1999) 23: 20–21.
25. Vatta M, Dumaine R, Varghese G, Richard TA, Shimizu W, Aihara N, Nademanee K, Brugada R, Brugada J, Veerakul G, Li H, Bowles NE, Brugada P, Antzelevitch C and Towbin JA: Genetic and biophysical basis of sudden unexplained nocturnal death syndrome (SUNDS), a disease allelic to Brugada syndrome. Hum Mol Genet (2002) 11: 337–345.
26. Bezzina C, Veldkamp MW, van Den Berg MP, Postma AV, Rook MB, Viersma JW, van Langen IM, Tan-Sindhunata G, Bink-Boelkens MT, van Der Hout AH, Mannens MM and Wilde AA: A single Na (+) channel mutation causing both long-QT and Brugada syndromes. Circ Res (1999) 85: 1206–1213.
27. Kyndt F, Probst V, Potet F, Demolombe S, Chevallier JC, Baro I, Moisan JP, Boisseau P, Schott JJ, Escande D and Le Marec H: Novel SCN5A mutation leading either to isolated cardiac conduction defect or Brugada syndrome in a large French family. Circulation (2001) 104: 3081–3086.
28. Nademanee K, Veerakul G, Nimmannit S, Chaowakul V, Bhuripanyo K, Likittanasombat K, Tunsanga K, Kuasirikul S, Malasit P, Tansupasawadikul S and Tatsanavivat P: Arrhythmogenic marker for the sudden unexplained death syndrome in Thai men. Circulation (1997) 96: 2595–2600.
29. Hong K, Berruezo-Sanchez A, Poungvarin N, Oliva A, Vatta M, Brugada J, Brugada P, Towbin JA, Dumaine R, Pinero-Galvez C, Antzelevitch C and Brugada R: Phenotypic characterization of a large European family with Brugada syndrome displaying a sudden unexpected death syndrome mutation in SCN5A. J Cardiovasc Electrophysiol (2004) 15: 64–69.
30. Brugada J, Brugada R, Antzelevitch C, Towbin J, Nademanee K and Brugada P: Long-term follow-up of individuals with the electrocardiographic pattern of right bundle-branch block and ST-segment elevation in precordial leads V1 to V3. Circulation (2002) 105: 73–78.
31. Priori SG, Napolitano C, Gasparini M, Pappone C, Della Bella P, Brignole M, Giordano U, Giovannini T, Menozzi C, Bloise R, Crotti L, Terreni L and Schwartz PJ: 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.
32. Priori SG, Napolitano C, Schwartz PJ, Bloise R, Crotti L and Ronchetti E: The elusive link between LQT3 and Brugada syndrome: the role of flecainide challenge. Circulation (2000) 102: 945–947.
33. Kanda M, Shimizu W, Matsuo K, Nagaya N, Taguchi A, Suyama K, Kurita T, Aihara N and Kamakura S: Electrophysiologic characteristics and implications of induced ventricular fibrillation in symptomatic patients with Brugada syndrome. J Am Coll Cardiol (2002) 39: 1799–1805.
34. Eckardt L, Kirchhof P, Schulze-Bahr E, Rolf S, Ribbing M, Loh P, Bruns HJ, Witte A, Milberg P, Borggrefe M, Breithardt G, Wichter T and Haverkamp W: Electrophysiologic investigation in Brugada syndrome; yield of programmed ventricular stimulation at two ventricular sites with up to three premature beats. Eur Heart J (2002) 23: 1394–1401.
35. Takenaka S, Kusano KF, Hisamatsu K, Nagase S, Nakamura K, Morita H, Matsubara H, Emori T and Ohe T: Relatively benign clinical course in asymptomatic patients with brugada-type electrocardiogram without family history of sudden death. J Cardiovasc Electrophysiol (2001) 12: 2–6.
36. Brugada J, Brugada R and Brugada P: Determinants of sudden cardiac death in individuals with the electrocardiographic pattern of Brugada syndrome and no previous cardiac arrest. Circulation (2003) 108: 3092–3096.
37. Antzelevitch C: The Brugada syndrome: ionic basis and arrhythmia mechanisms. J Cardiovasc Electrophysiol (2001) 12: 268–272.