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Diagnostic and genetic aspects of the Brugada and other inherited arrhythmias syndromes

Charles Antzelevitch, PhD^{a,*}, Arthur Wilde, MD, PhD^b, Lars Eckardt^c, Masayasu Hiraoka, MD, PhD^d, and Domenico Corrado, MD^e

^aMasonic Medical Research Laboratory, Utica, NY, USA ^bAcademic Medical Center, University of Amsterdam, Amsterdam, The Netherlands ^cHospital of the Westfälischen Wilhelms-University, Department of Cardiology and Angiology and Institute for Arteriosclerosis Research, Münster, Germany ^dLabour Insurance Appeal Committee Ministry of Health, Labour and Welfare of Japan, Tokyo, Japan ^eDivision of Cardiology, University of Padova, Padua, Italy

Abstract

Doctor Wilde, presenting on behalf of himself and Dr Eckardt, discussed the role of invasive and noninvasive tests for risk stratification of Brugada syndrome. Doctor Hiraoka, presenting on behalf of Y. Yokoyama, M. Takagi, N. Aihara, K. Aonuma, and the Japan Idiopathic Ventricular Fibrillation Study Investigators, further discussed the diagnostic criteria for the Brugada syndrome. Doctor Antzelevitch examined the hypothesis that amplification of spatial dispersion of repolarization in the form of transmural dispersion of repolarization underlies the development of life-threatening ventricular arrhythmias associated with inherited ion channelopathies including the long QT, short QT, and Brugada syndromes. Doctor Corrado discussed the relationship between channelopathies and heart muscle diseases.

Keywords

Arrhythmia; Sudden cardiac death; Ventricular tachycardia; Fibrillation; Electrophysiology; Channelopathies

Role of invasive and noninvasive tests for stratification (A. Wilde and L. Eckardt)

Brugada syndrome is increasingly recognized as a disease entity associated with sudden cardiac death (SCD), most often, in relatively young individuals without structural heart disease. The typical ECG is characterized by right precordial ST-segment elevation and discrete prolongation of diverse conduction parameters. Three types of ST-segment elevation are recognized, but only one, type 1 (ie, the 'coved-type' ST segment), is considered to be diagnostic of Brugada syndrome. When a type 1 ECG is associated with documented (or inducible) ventricular arrhythmias, premature SCD or similar ECGs in family members, or nocturnal agonal respiration, Brugada syndrome is diagnosed.^{1,2} When the ECG is absent at baseline, drug challenge (iv flecainide, ajmaline procainamide, pilsicainide, or other sodium channel blockers) can unmask the ECG features. A genetic diagnosis can identify 18% to 30% of patients with SCN5A mutations. It is not essential for definitive diagnosis of the syndrome.

* Corresponding author. Masonic Medical Research Laboratory, Utica, NY 13501-1787, USA. Tel.: +1 315 735 2217; fax: +1 315 735 5648. E-mail address: ca@mmrl.edu.

The risk for malignant ventricular arrhythmias in Brugada patients with a spontaneous or drug-induced coved-type ECG is ill-defined. There is only one study on the population level that disclosed a significantly increased lifetime risk for unexpected sudden death (Japan). General agreement exists that successfully resuscitated or otherwise symptomatic patients (with a type 1 ECG) are at significant risk for recurrent, potentially lethal, events, and implantable cardioverter defibrillator (ICD) therapy is undisputed. Yet, the risk estimates differ significantly between different series. The highest risk is encountered in a series on 334 patients reported by Brugada et al (higher than 35%), whereas Priori et al and Eckardt et al report a risk of around 5%, all with roughly similar follow-up duration and a comparable number of symptomatic patients in the series (for references, see the literature list in Eckardt et al³).

The situation is less clear for asymptomatic patients with a spontaneous type 1 ECG. Both risk and risk predictors are disputed. Brugada et al demonstrated a significantly increased risk for sudden death (or its presumed equivalent an appropriate ICD intervention) of over 25% in their initial series and 5% in their last report on 263 patients (follow-up duration, 31 ± 41 months; all patients with a spontaneous type 1 ECG). Eckardt et al³ demonstrated in 70 patients a risk of 1.4% (follow-up, 40 ± 50 months). Programmed electrical stimulation (PES) was shown to possess strong predictive power by Brugada et al, whereas the studies by Priori et al and Eckardt et al were not able to reproduce these results.

In a recent meta-analysis on this topic, Gehi et al⁴ pooled 19 studies, including the 3 studies previously mentioned that accounted for most patients. The pooled data of a relevant selection of these studies revealed a significant increased risk for future events (syncope, SCD, or ICD shock) for the spontaneous type 1 ECG (versus the drug-induced ECG), the presence of symptoms, and the male sex. Inducibility with programmed electrical stimulation and the family history for SCD did not reach significant predictive power. In addition, the presence of a SCN5a mutation seemed not to be relevant for risk stratification. The prognostic role of programmed electrical stimulation was also tested by Paul et al⁵ from 13 clinical trials with more than 10 patients and clinical data including event rate available; 1140 patients were pooled. The odds ratio for inducibility of sustained ventricular tachycardia (VT) during PES (523 of the 966 patients that underwent PES) in relation to VT/VF recurrences during follow-up was 1.067 ($P < .937$) for all studies together, 10.002 ($P < .0001$) for the study reported by the Brugada et al, and 0.910 ($P < .916$) for all other studies including the previously mentioned 2 other larger studies. These data show that risk stratification in patients with Brugada syndrome is not that clear. The reasons for the discrepancies are unknown and can only be speculated upon. One potential reason at least is a bias toward more severe cases in the Brugada registry, but at the present, this is merely speculation. Further studies will be needed to settle this issue, and in particular, a longer follow-up duration is obligatory before sound conclusions can be drawn. Attention should at the same time be paid to noninvasive markers. Data from relatively small recent series provide evidence that, in particular, daily fluctuations in the magnitude of the right precordial ST-segment elevation and in the appearance of late potentials might possess predictive power for future events.^{6,7}

Diagnostic criteria for the Brugada syndrome (M. Hiraoka)

Patients with the Brugada syndrome have a high risk of having SCD. Although many display an ST elevation in V1-V3 without developing VF, definitive diagnostic criteria capable of identifying patients with Brugada syndrome at risk for SCD have yet to be established. Two consensus reports have appeared proposing diagnostic criteria and risk stratification schemes.^{1,2,8,9} The proposed criteria stress spontaneous and drug-induced appearance of type 1 (coved-type) ST elevation (the European Society of Cardiology [ESC] criteria), but it is not certain whether the drug-induced type 1 ST elevation can identify patients with the Brugada syndrome from other group of patients and predict a high risk for development of cardiac events (VF,

syncope, and/or SCD). A multicenter study, named the Japan Idiopathic Ventricular Fibrillation Study (J-IVFS), was recently conducted to assess diagnostic accuracy and to predict cardiac events by drug challenge in patients with the Brugada syndrome and suspected cases of Brugada syndrome. Among 217 enrolled cases, 89 underwent a pilsicainide challenge (class IC agent) administered iv. Their mean age was 51.2 years, with 44 cases showing symptomatic (syncope or documented VT/VF), and 45 asymptomatic.

Three distinct groups were considered based on ST elevation: coved (C), saddleback (S), and undefined (U), which were not included in C and S. After the pilsicainide test, 42% of 89 cases changed to type 1 (C), but 52% stayed in non-coved-type (S and U). The consensus conference criteria showed sensitivity of 38.6%, even in symptomatic patients. When J point elevation higher than 2 mm was considered, irrespective of the type of ST elevation induced by sodium block challenge (J-IVFS criteria), sensitivity increased to 61.4%. Fifty-three cases were followed for a mean of 34 months, and 13 cases experienced cardiac events. Four of these cases showed type 1 ST-segment elevation after drug administration, but 9 exhibited non-coved-type ST elevation (S and U). Prediction of cardiac events by consensus conference criteria provided a sensitivity of 30.8%, whereas the J-IVFS criteria increased sensitivity to 53.8%. These results suggest that the requirement for a type 1 ST elevation after drug challenge can lead to an underestimation of diagnosed cases of Brugada syndrome as well as an underestimation of those at risk.

Long QT syndrome, Brugada syndrome, and conduction system disease: what is the link? (C. Antzelevitch)

In the long QT syndrome, amplification of transmural dispersion of repolarization (TDR) is often secondary to preferential prolongation of the action potential duration (APD) of M cells, whereas in the Brugada syndrome, it is thought to be due to selective abbreviation of the APD of right ventricular (RV) epicardium. Preferential abbreviation of APD of either endocardium or epicardium appears to be responsible for amplification of TDR in the short QT syndrome. These 3 inherited sudden death syndromes display different characteristics of the QT syndrome.¹⁰

In the long QT syndrome, the QT interval increases as a function of disease or drug concentration.¹¹ In the Brugada syndrome, QT interval is largely unchanged,¹² and in the short QT syndrome, the QT interval abbreviates as a function of disease or drug concentration.¹³ What they all have in common is the development of an augmented spatial dispersion of repolarization, TDR in particular. When TDR reaches the threshold for reentry, polymorphic VT develops. In the setting of long QT syndrome, we refer to it as torsade de pointes.¹⁰

It is noteworthy that the threshold for reentry occurs at progressively shorter TDR values for long QT, Brugada, and short QT syndromes because of progressively abbreviated refractoriness. In conclusion, the long QT, short QT, and Brugada syndromes are pathologies with very different phenotypes and etiologies but which share a common final pathway in causing sudden death.

Is the Brugada syndrome a cardiomyopathy? (D. Corrado)

The limits between inherited primary electrical heart diseases (channelopathy) and structural heart muscle disease (cardiomyopathy) remain largely undefined.

Brugada syndrome has been initially described as an ECG-defined condition characterized by a distinctive ECG pattern of right bundle branch block and right precordial ST-segment elevation, and it has been associated with the risk of ventricular fibrillation and sudden death.

¹⁴ Although Brugada et al advanced that the syndrome was primarily an electrical heart disorder, other authors reported a clear relationship between the ECG pattern of right bundle branch block and right precordial ST-segment elevation to an RV cardiomyopathy.^{15,16} In 1989, Martini et al¹⁵ described 6 patients with apparently idiopathic ventricular fibrillation, 3 of whom had the ECG pattern of early repolarization in right precordial leads. In these patients, underlying structural abnormalities of the right ventricle were clinically documented. Corrado et al¹⁶ provided definitive evidence that a familial structural heart disease affecting both the RV myocardium and the specialized conduction system may present clinically as ‘right bundle branch block (RBBB), right precordial ST-segment elevation, and sudden death’ syndrome. The debated nature of the syndrome has evolved over the last 15 years into the current perspective of a genetically determined channelopathy, with demonstration of a genetically defective sodium channel gene in up to one third of cases.^{8,9} A plausible explanation for the initially conflicting interpretation of the etiopathogenesis of the Brugada syndrome has been in part provided by a clinicopathologic study that addressed prevalence, substrates, and clinical profile of young sudden death victims with the ECG pattern of right precordial ST-segment elevation.¹⁷ Among a series of 273 young victims of cardiovascular sudden death who were prospectively studied from 1979 to 1998 in the Veneto Region of Italy, 12-lead ECG was available in 96 cases (36%). Right precordial ST-segment elevation was found in 14% of young sudden death victims with available ECG, and this ECG pattern characterized a subgroup of patients with an underlying RV cardiomyopathy who showed a propensity for SCD from non-exercise-related cardiac arrest and to exhibit dynamic ECG changes and polymorphic ventricular tachycardia, all clinical and ECG features typically observed in Brugada syndrome. There are several possible explanations for the observed phenotype overlap between RV cardiomyopathy and Brugada syndrome.¹⁸ First, the lesions predominantly involved the epicardial and midmyocardial layers of the right ventricle and created a transmural gradient of myocyte degeneration and death in the setting of the fibrofatty replacement. This pathologic substrate potentially accounted for a ‘structural’ epicardial-endocardial heterogeneity of repolarization in the RV wall, predisposing to “phase 2 reentry,” as in Brugada syndrome. Second, RV structural changes could be a consequence of a genetically defective cardiac sodium channel, which in time can induce myocyte death. In this regard, familial Lenègre disease (also known as ‘progressive cardiac conduction disease’), which is a progressive disease of the specialized conduction tissue and characterized by fibrofatty atrophy of the His-Purkinje system, has been recently linked to mutations in SCN5A, the same gene involved in channelopathies such as Brugada syndrome and the LQT3 variant of long QT syndrome. Third, a double genetic defect could account for the coexistence of both Brugada and RV cardiomyopathy phenotypes.

For years, cardiomyopathies were defined as heart muscle disease of unknown cause and were classified according to their peculiar phenotypic expression and pathophysiological features as dilated (in the setting of dilatation and poor contractility of the ventricles), hypertrophic (in the presence of unexplained hypertrophy of the left ventricle), restrictive (when endocardial thickening and cavity obliteration hinder diastolic ventricular filling, and arrhythmogenic RV (with selective morphofunctional RV abnormalities associated with ventricular arrhythmias predisposing to sudden arrhythmic death).^{18,19} The recent development of molecular genetics, with the discovery of a genetic role in syndromes of previously unknown origin, raised the need for a new classification that goes beyond the phenotype. Inherited cardiac ion channel diseases are genetically determined primary myocardial electrical diseases that do not have major structural abnormalities as features. Nonetheless, the myocyte is abnormal, although the heart is grossly structurally intact. The genetic variation responsible for the channelopathy, however, does often lead to a structural defect in the microstructure of the heart at the level of the ion channel. Hence, these life-threatening cardiac dysfunctions, causing a high risk of arrhythmic sudden death, should be included among the listing of cardiomyopathies. The new definition/classification of inherited cardiomyopathies of the task force of the American Heart

Association (AHA) takes into account the underlying gene mutations and the cellular level of expression of encoded proteins.²⁰ The consistent type of protein alteration supports the concept of “final common pathway” of genetically determined cardiomyopathies, hypertrophic cardiomyopathy being deemed to be a sarcomeric cardiomyopathy; dilated cardiomyopathy, a cytoskeletal cardiomyopathy; arrhythmogenic RV cardiomyopathy, a desmosomal cardiomyopathy; and Brugada syndrome, an ion channel cardiomyopathy.

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