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Editorial Comment

J-Wave Syndromes Caused by Repolarization or Depolarization Mechanisms

A Debated Issue Among Experimental and Clinical Electrophysiologists*

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The J-wave deflection occurring at the QRS-ST junction (also known as Osborn waves) was first described in 1953 and is seen in many conditions such as hypothermia; hypercalcemia; brain injury; vasospastic angina; acute ischemia, especially in true posterior myocardial infarction with occlusion of the left circumflex coronary artery; Brugada syndrome (BrS); and early repolarization syndromes (1).

BrS is associated with syncope and/or sudden cardiac death caused by ventricular tachycardia or fibrillation (2). This syndrome is diagnosed with a type 1 electrocardiogram (ECG) if the coved-type ST-segment elevation occurs either spontaneously or after provocation tests with class I antiarrhythmic drugs. If a patient is asymptomatic for ventricular tachyarrhythmias or syncope and a typical coved type 1 ECG is obtained, this is termed a Brugada ECG pattern (3,4).

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The normal surface ECG is the result of temporal changes in depolarization and repolarization processes. Cardiac depolarization is denoted by the QRS complex, whereas repolarization includes the J-wave, ST-segment, T-wave, and U-wave. Despite substantial progress in our understanding of cardiac electrophysiology, the cellular basis of the normal resting ECG has not been fully explored.

The underlying mechanisms of the diagnostic coved-type ECG obtained in BrS have also been debated for a long time by both experimental and clinical electrophysiologists. Two major hypotheses underlying the basis of the type 1 Brugada ECG pattern emerged: "the depolarization disorder hypothesis" (5) and "the repolarization disorder hypothesis" (6,7). In principle, BrS is a cardiac disease that involves the right ventricle only. This is evidenced by diagnostic electrocardiographic changes recorded in the right precordial leads (3,4); structural changes in the right ventricle such as localized fibrosis, right ventricular outflow tract (RVOT) enlargement, and the presence of slightly reduced right ventricular functional parameters (8); ventricular tachycardia/ventricular fibrillation originating in the right ventricle (usually the RVOT) (9); and spontaneous ventricular tachycardia preceded by conduction heterogeneity in the RVOT (mainly the epicardium) (10).

Antzelevitch et al. (11–14) have performed elegant experimental work over the past 10 years and contributed a number of milestone articles that substantially improved our understanding of the normal and pathological electrocardiographic changes under various conditions. Physiological heterogeneity of electrical properties and transmural gradients in ion channel distribution in the endocardial, midmyocardial (M cells), and epicardial layers result in regional differences in electrophysiological properties. Ventricular epicardial and M cells, but not endocardial action potentials, display a prominent phase 1 due to a large transient outward potassium current (I_{to}) giving rise to the typical spike-and-dome or notched configuration of the action potential. The magnitude of I_{to} and degree of action potential notch differ also between right and left ventricular epicardial and M cells, with right ventricular cells displaying a much greater I_{to}. The unequal distribution of I_{to} is supposed to contribute to the transmural gradient in the action potential configuration and the voltage gradient across the right ventricular wall is likely to contribute to the inscription of the J-point elevation and coved-type ECG pattern in patients with BrS. Furthermore, in canines, the prominent epicardial action potential notch (large I_{to}) is shown to be associated with a greater predisposition to all-or-none repolarization and phase 2 re-entry. This is because propagation of the action potential dome from sites at which it is maintained to sites at which it is reduced or abolished can cause local re-excitation with bursts of extrasystolic beats, which may initiate re-entry. These experimental findings form the basis

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of the "repolarization disorder hypothesis," possibly underlying the coved-type ECG in patients with BrS. Bloch Thomsen et al. (15) recently provided clinical evidence in humans that the accentuation of epicardial action potential and loss of dome underlie the ST elevation and arrhythmogenic substrate associated with BrS.

In this issue of the *Journal*, Postema et al. (5) put forward another explanation responsible for the typical Brugada electrocardiographic changes in support of the "depolarization disorder hypothesis" using 3 noninvasive electrocardiographic approaches (electrocardiography, vectorcardiography, and body surface potential mapping) in parallel in patients undergoing intravenous drug challenge with ajmaline (5). A type 1 ECG was induced in 91 patients, and 162 patients with a negative test result served as controls. BrS patients with a coved-type ECG revealed depolarization abnormalities that were mapped to the right ventricle and exhibited longer right precordial filtered QRS duration and right terminal conduction delay. Repolarization abnormalities remained concordant with depolarization abnormalities and similar T_{peak}-T_{end} and comparable T_{peak}-T_{end} dispersion were measured. Using these noninvasive electrocardiographic techniques, the authors conclude that the type 1 Brugada ECG is characterized predominantly by localized depolarization abnormalities in the absence of repolarization abnormalities. These provocative *clinical* findings reinitiate the discussion about the mechanisms underlying the coved-type diagnostic Brugada ECG.

The list of arguments supporting the "depolarization disorder hypothesis" is long, but not conclusive. Clinically, patients with a type 1 Brugada ECG positive for sodium channel (*SCN5a*) mutations reveal a longer PR interval and QRS duration and deeper S waves in the inferior leads than negative *SCN5a* carriers (16). Atrial conduction times are typically prolonged in patients in whom BrS is associated with spontaneous atrial fibrillation. In post-mortem studies, localized fibrosis can be found in the right ventricle of patients with BrS (17). Patients undergoing detailed endocardial mapping using CARTO demonstrate significant slowing of conduction, especially in the RVOT (18). Various studies found right ventricular conduction delays (late potentials) preferentially in the right precordial leads (19–21). Surface electrocardiographic measurements of repolarization using T_{peak}-T_{end} as an indicator of transmural heterogeneity of repolarization are absent in patients with BrS (5). Clinically, patients with recurrent syncope and a coved-type ECG may benefit from implantable cardioverter-defibrillator (ICD) therapy. The clinical observation that in the absence of documented ICD interventions for ventricular tachycardia/ventricular fibrillation patients may remain free of syncope suggests that intermittent heart block, which is a potential mechanism for syncope, especially in patients with *SCN5a* mutations, may be prevented (M. Borggrefe and C. Wolpert, unpublished clinical observation, August 2007).

Now we are exposed to 2 divergent views on the fundamental mechanisms underlying the coved-type diagnostic Brugada ECG that are supported by experimental work and a limited number of clinical case studies: the basic scientists' view ("repolarization disorder hypothesis") and the clinical electrophysiologists' view ("depolarization disorder hypothesis") substantiated by a number of clinical observations using crude technical measures such as surface electrocardiography, vectorcardiography, body surface potential mapping, and signal averaging. These diverse standpoints are indicative of our limited knowledge of the molecular basis and clinical presentation of a major clinical problem. Currently, we cannot clearly differentiate the clinical phenotypes of BrS patients. Despite the fact that clear definitions are given in the 2 Brugada consensus papers, the typical coved-type ECG is often not present, even in illustrations of electrocardiographic tracings accompanying elegant scientific work on the pathophysiology of BrS (3,4). If the clinical phenotype and the molecular basis are not clear, genotyping of the patients for a specific gene is not expected to provide a useful diagnostic tool. The latter is reflected by the low diagnostic yield of genetic testing in BrS in which only as many as 20% of patients are currently genotyped. This is in contrast to patients with long QT syndrome in which the phenotype is much clearer and genetic testing is able to provide a positive genotype in more than 70% of the patients.

In conclusion, the molecular basis and the clinical manifestations of BrS are still incompletely understood and the current debate on depolarization versus repolarization disorder hypotheses clearly illustrates the urgent need for further experimental studies in suitable animal models and clinical studies in affected individuals to better understand the mechanisms underlying BrS.

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Key Words: Brugada syndrome ■ sudden cardiac death ■ electrocardiography ■ body surface potential mapping ■ vectorcardiography.