Commentary on the Brugada ECG Pattern
A Marker of Channelopathy, Structural Heart Disease, or Neither?
Toward a Unifying Mechanism of the Brugada Syndrome

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“Simplicity may be beauty in art, but Science is complex beauty that cannot be reduced into simplicity.”
—Pedro Brugada

In this issue of Circulation: Arrhythmia and Electrophysiology, Hoogendijk and coworkers review a part of the available knowledge on Brugada syndrome and attempt to find a unifying mechanism for the pathophysiologic basis of this disease. This exercise is very interesting from a scientific point of view, but it may be too premature.

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Eighteen years after the initial description of 8 patients with what has become known as Brugada syndrome, this disease has changed from an ECG curiosity to a diagnosis to be considered in the everyday practice of cardiology in patients with resuscitated sudden cardiac death; in patients with syncope of unknown origin; and in patients with lone atrial fibrillation, particularly the familial forms. With the increasing number of patients being diagnosed with Brugada syndrome, our knowledge also has grown in every single aspect of this disease. Today, we understand that there is (1) great variability in clinical presentation of the disease, (2) that the ECG manifestations are solely the phenotype of a variety of etiologies, (3) that there is enormous genetic heterogeneity, and (4) that we may be dealing with a variety of diseases with the same manifestations and not only one single disease. If the latter is true, a single mechanism can never explain the whole spectrum of the disease.

Brugada syndrome has a large variation in clinical presentation. Carriers of the disease (as proven by a coved-type Brugada ECG, no gross cardiac structural abnormalities, mutation analysis, and absence of other diagnoses) can remain completely asymptomatic and die from unrelated conditions. On the other hand, patients with apparently the same characteristics can die suddenly at first manifestation of the disease. In between these two extremes we encounter individuals who develop atrial fibrillation or flutter as a sole manifestation and individuals with syncopal episodes that can be caused by a variety of arrhythmias, such as sick sinus syndrome, rapid or slow atrial fibrillation, conduction disturbances, ventricular tachycardia or fibrillation, or a combination of these. What exactly determines the clinical presentation is unknown. We also do not know in general why the arrhythmias occur at a certain moment aside from clear triggers like fever or some drugs. We are just starting to understand that a patient with a spontaneous coved-type ECG carries a poorer prognosis than the patient in whom the coved-type ECG is only present after the administration of a sodium channel blocker. All registries agree on this point as well as on the poor prognosis of the patient with Brugada syndrome and syncope. It is tempting to speculate that the degree of dysfunction of the affected cardiac channel determines the clinical presentation. In the case of the sodium channel, preliminary data show that carriers of mutations leading to a truncated protein have a 6-fold increase in the risk of sudden death or resuscitated ventricular fibrillation compared with carriers of mutations not truncating the protein. A possible pathophysiological interpretation of this observation is that carriers of mutations leading to a truncated protein have a major loss of function of the cardiac sodium channel and, therefore, a worse prognosis.

The ECG manifestations of Brugada syndrome are solely the phenotype of a multitude of possible etiologies. Essential for the diagnosis of Brugada syndrome is the exclusion of other etiologies of ST-segment elevation that could mimic Brugada syndrome. The list of diseases and conditions causing ST-segment elevation is long, and these diseases and conditions have to be excluded before a diagnosis of Brugada syndrome is made. We can compare this situation to atrial fibrillation. The ECG manifestations of atrial fibrillation are practically the same for a large variety of etiologies from hypertensive heart disease, cardiomyopathies, and hyperthyroidism to lone atrial fibrillation. When confronted with a familial form of lone atrial fibrillation, all other etiologies are excluded first before the diagnosis “lone” atrial fibrillation is made. Thus, it makes no sense to state that Brugada syndrome can appear after ajmaline in Chagas disease. It is the coved-type ECG that appears in Chagas disease; thus, the patient has Chagas disease not Brugada syndrome. Of course, the single case in which this retrospective observation was made almost 30 years ago may have suffered from two diseases: an infectious one and a hereditary one.

With regard to genetic heterogeneity, an international compendium of mutations in the SCN5A gene encoding for the sodium channel has been published recently. A total of 293 different mutations were found in 2111 unrelated indi-
individuals. Data came from 9 centers worldwide, each having genotyped at least 100 probands with Brugada syndrome. Mutations were found in 10% to 20% of the patients. Thus, in the remaining 80% to 90%, the causes of the ECG and clinical manifestations remain unknown. If the exact etiology is unknown in the majority, it is extremely speculative to try the search for a unifying mechanism for Brugada syndrome based on the limited available cellular electrophysiology data of the known mutations. (For the available mutations, cellular electrophysiology data exist just for a few.) It is highly probable that all these different mutations have different cellular electrophysiological effects. These different effects also could explain why some mutations are temperature sensitive and others are not. The same could explain why some patients in some countries seem to respond to quinidine10 whereas other populations with another genetic background and other mutations do not respond to the drug. In our first publication of three different mutations in the sodium channel in 1998,11 we discussed the possibility that different mutations give different clinical and ECG manifestations. The recent observations made on the worse prognosis of patients with mutations leading to a truncated protein come to support this hypothesis. It is clear that we still have a long way to go before understanding every little detail of Brugada syndrome.

If we have different mutations in the same SCN5A gene and other mutated genes that lead to the same clinical and ECG manifestations, and if we do not know the cause of the syndrome in the large majority of patients, are we dealing with a multitude of different diseases that lead to a common phenotype? Is that not comparable to the multitude of variations of left ventricular hypertrophy on echocardiography or the atrial fibrillation waves on the surface ECG? We do not search for a unifying mechanism for the different hypertrophic hearts when we understand the specific underlying mechanisms. Similarly, we do not search for a single hypothesis of mechanisms in the different well-characterized etiologies of atrial fibrillation. To illustrate these limitations in our knowledge, 2 12-lead ECGs in 2 patients with Brugada syndrome are shown in Figure. Both show the typical coved-type ST-segment elevation in leads V1 to V2. However, the ECG in Figure 1A has additional features that are absent on the ECG in Figure 1B: a prolonged PR interval, a wide QRS complex with a true right-bundle branch block, and an ST-segment elevation in lead aVL. We may think that the patient represented in Figure 1A has a worse ECG and, therefore, a worse prognosis than the patient in Figure 1B. The patient in Figure 1A was asymptomatic and received a prophylactic implantable cardioverter defibrillator because of inducible ventricular fibrillation during the electrophysiological study. He has no had events in the so-far 16 years of follow-up. In contrast, the patient in Figure 1B received an implantable cardioverter defibrillator after he was resuscitated from spontaneous ventricular fibrillation—the first manifestation of his disease.

It is our lack of knowledge on the exact causes of Brugada syndrome that promotes scientific speculation. Speculation will decrease as our knowledge advances. It is because of the limited knowledge available on Brugada syndrome today that I believe that searching for a unifying mechanism in 2010 is premature. Hoogendijk and coworkers have to be congratulated on a really worthy scientific effort that will require periodic repetition.

Disclosures

None.

References


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