Editorial

Brugada Syndrome
Why Are There Multiple Answers to a Simple Question?

Ramon Brugada, MD; Robert Roberts, MD

In 1986, two young brothers who survived documented cardiac arrests exhibited a specific electrocardiographic pattern providing a link to sudden death. Similar observations in other individuals led to the original description in 1992 of the syndrome consisting of right bundle branch block, ST-segment elevation in leads V1 to V3, and sudden death with structurally normal heart—i.e., the Brugada syndrome.1 This syndrome has stimulated research in many centers. What before was an electrocardiographic pattern resembling early repolarization has now become a marker for increased risk of sudden death. Fortunately, this observation coincided with an outpouring of molecular research in cardiology and with the success already encountered in identifying the genetic basis of other arrhythmic diseases. Brugada syndrome likely will continue to benefit from the application of genomics. In just 10 years, the disease has become widely recognized, and researchers in multiple disciplines in basic and clinical research have come together to decipher its pathogenesis.

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The most common presentation is a middle-aged man, with the electrocardiographic blueprint, no structural heart disease, and a documented history of ventricular fibrillation.2 In 1997, Nademanee et al3 linked Brugada syndrome to sudden unexpected death syndrome (SUDS) in Southeast Asia. SUDS has been recognized since the 1980s, when the Centers for Disease Control reported a higher than usual incidence of sudden death in individuals from that geographic area.4 The individuals usually die during their sleep from ventricular tachyarrhythmias. In some countries, SUDS is an important cause of death in young males, second only to car accidents. The electrocardiographic pattern is the same as that seen in Brugada syndrome, indicating that SUDS and Brugada syndrome are similar diseases, if not the same.3 A sex difference in Brugada syndrome is obvious in Southeast Asia, where only males are symptomatic. In Europe, the sex difference is not as distinct. The association between Brugada syndrome and sudden infant death syndrome (SIDS), which had been suspected since the original description, also has been confirmed.5

Insight from cellular electrophysiology suggests that ST-segment elevation is caused by a shift in the ionic current balance and the creation of a voltage gradient, with predominance of the transient outward current (Ito) in the epicardium over the endocardium.6 A difference in the pattern of expression of this current in the right ventricle versus the left ventricle accounts for the presence of the electrocardiographic pattern solely in the right precordial leads.6 Without a doubt, however, genetics afforded the basis to integrate the clinical phenotype with the cellular electrophysiology by identifying responsible mutations in the gene that encodes for the cardiac sodium channel, SCN5A.7 This genetic basis has proven that the disease is a channelopathy and primarily an electrical disease. Electrophysiological analysis shows that mutated channels inactivate faster or are nonfunctional.7 These nonfunctional channels, which act in phase 0 of the action potential, leave Ito currents unopposed in phase 1, creating a transmural voltage gradient and a substrate for reentrant arrhythmias. Electrophysiological analysis has also indicated worsening of function at higher temperatures in some mutations.8 This may explain why some patients present with ventricular fibrillation during febrile episodes.

Diagnosis and risk stratification were not to remain as simple as they seemed. The typical clinical presentation of the middle-aged patient with a classic ECG and aborted sudden death has now been confounded with the identification of asymptomatic individuals, family members, and transient normalization of the ECG in some patients.9 Everyone agrees that there is a high risk of recurrence of cardiac arrest; therefore, symptomatic individuals require some form of protection.5 Some investigators advocate guinidine, although others prefer an implantable cardioverter-defibrillator.2 Asymptomatic individuals present a greater dilemma. One must expect events to occur in these individuals because symptomatic patients usually have been asymptomatic for many years. The question is, who? And when? It seems from the latest follow-up that programmed electrical stimulation (PES) will help to predict who is at risk.10

The degree and type of ST-segment elevation (coved versus saddle-back) and transient normalization are issues that are presently being investigated to assess whether they afford better risk stratification. The normalization of the ECG represents an important diagnostic challenge. Fortunately, investigators have described the induction of electrocardiographic alterations with autonomic factors or the use of antiarrhythmics.11 The latter, in the form of class I agents, have since become an important diagnostic tool. The diagnostic specificity and sensitivity of the antiarrhythmic drug

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From the Section of Cardiology, Baylor College of Medicine, Houston, Tex.

Correspondence to Robert Roberts, MD, Don W. Chapman Professor of Medicine, Professor of Medicine and Cell Biology, Department of Medicine, Section of Cardiology, Baylor College of Medicine, 6550 Fannin, MS SM677, Houston, TX 77030. E-mail rroberts@bcm.tmc.edu

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challenge was assessed in individuals who carried SCN5A mutations and in patients with transient normalization of the ECG. The infusion of ajmaline was shown to be highly accurate in identifying affected individuals.\textsuperscript{12} Reports of false-negative studies, however, have challenged its specificity.\textsuperscript{13} The diagnostic challenge is further complicated by the fact different drugs are approved for use in different countries, and each physician is obliged to use what is available. It is accepted, though, that ajmaline is the most potent antiarrhythmic, followed by flecainide, with procainamide the least likely to uncover the electrocardiographic abnormality.

While identification of the genetic defects in SCN5A has clarified the molecular basis of Brugada syndrome, the field of genetics was casting shadows in other directions. The sodium channel determines the upstroke or phase 0 of the action potential in atrial and ventricular cells. This rapid inward sodium current predominates in cardiac depolarization. Therefore, it perhaps was expected that different mutations in the gene that encodes for SCN5A would be linked to multiple arrhythmic diseases. Mutations in \textit{SCN5A} were shown to induce Brugada syndrome, idiopathic ventricular fibrillation, isolated cardiac conduction defect (ICCD),\textsuperscript{14} and long-QT syndrome (LQT3).\textsuperscript{15} Our hope was that genetics actually would help to distinguish among the different diseases. So it seemed at the beginning, when analysis of the mutations indicated that in some way LQT3 and Brugada syndrome could be considered mirror images, with faster inactivation or a nonfunctional channel in Brugada syndrome\textsuperscript{2} and delayed inactivation with persistent current in LQT3.\textsuperscript{15} Then, a family was described that had the same mutation and 2 different phenotypes: some members had LQT3, and others, Brugada syndrome.\textsuperscript{16}

The study by Kyndt et al\textsuperscript{17} in the present issue of \textit{Circulation} is an illustrative example of the same mutation inducing either Brugada syndrome or a conduction defect, which emphasizes the complexity of a single-gene disease. Despite the fact that the 13 individuals in this study have the same mutation in \textit{SCN5A}, 4 have a phenotype of Brugada syndrome; 8, ICCD; and 1, a completely normal ECG. The loss of function caused by the mutation leaves the gene carriers with half the normal amount of sodium current. This indicates that despite the fact that these are monogenic diseases and originate from the same mutation, the specific phenotype depends not only on the site of involvement of the sodium channel, but probably also on the balance between the different ionic currents. The alteration in overall current balance may be caused by the expression of minor differences in the genes responsible for these currents. It is well recognized that the phenotype of single-gene disorders may be modified by slight differences in other genes and by environmental stimuli. These minor genetic differences, referred to as polymorphisms, comprise an area of active research in identifying modifier genes and understanding polygenic disorders.\textsuperscript{18} It seems, therefore, that it is the level of alteration of the ionic balance that determines the risk of sudden death in these \textit{SCN5A} mutations. This is a hypothesis that has been advocated in recent years, and it is in accordance with certain clinical observations. Individuals who require sodium channel blockers to induce the electrocardiographic pattern seem to have the least level of alteration in the ionic balance and, so far, have a better prognosis than do individuals with abnormal ECG at baseline.\textsuperscript{19}

The sex difference in the long-QT and Brugada syndromes has been puzzling. The study by Kyndt et al\textsuperscript{17} rekindles this important debate. It appears that among gene carriers, males have a Brugada phenotype or a higher degree of impaired conduction than do females. Do estrogen, progesterone, or other hormones affect the expression of cardiac ionic channels? Do women require a higher level of alteration of the ionic balance to develop the disease? It seems so, and although fascinating, it is also a testable hypothesis. There is always the challenging exception, however—for example, individual III-13, male, who carries the mutation but has a normal ECG.

Lastly, but probably most important to the clinician, this family raises ethical, diagnostic, and therapeutic issues. The field of genetics is emerging as the gold standard in the diagnosis of monogenic diseases. There is now proof in this family that several individuals carry a mutation that has been linked to malignant arrhythmias and probably to sudden death in some of its members. Is patient III-13 entitled to know that he is a carrier of the mutation? Just as importantly, who at this point needs protection? Not all clinicians would come to the same conclusion. Some advocate the use of class I antiarrhythmics to unmask the syndrome; they attach prognostic value to PES and thus believe that ICCD patients have a better prognosis because of the negative flecainide test and negative PES.\textsuperscript{10} Other investigators think flecainide and PES are not so reliable.\textsuperscript{13} Therefore, can one assume that individuals with ICCD, negative flecainide test, and negative PES are at lower risk? We must accept that the specific phenotype does not depend solely on the predominant mutation, but one thing is true: All are carriers of a potentially malignant mutation.

Unfortunately, only time, events, and further clinical and basic research will be able to answer these questions. We must not downplay the progress provided by genetic findings. This disease is caused in part by defects in the gene for the \textit{SCN5A} channel, and thus we must avoid antiarrhythmics that inhibit the sodium channel. Second, we now have a specific molecular target to aid in the development of more precise and appropriate therapy. Third, a genetic diagnosis, though presently available only in highly specialized centers, with improved technology can be expected to be a routine test in the future. Thus, at this time, it remains for the physician to determine the ultimate treatment on the basis of the available diagnostic tools for risk stratification.

What started as a simple clinical description has become the fodder of thorough investigations that use the tools of the clinician, molecular biologist, and electrophysiologist. In 10 years we have achieved a certain level of knowledge and comfort in the basic aspects of this disease. There remain, however, many controversial issues and many more questions that defy our ability to understand, diagnose, and treat this complex biological process. There is nothing better than unanswered questions to stimulate much-needed research,
with the hope that this soon will provide an accurate diagnosis and more effective treatment.

References

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