The report of the Second Consensus Conference, published in Circulation in 2005, defined the Brugada syndrome as ST-segment elevation in the right precordial ECG leads (so-called type 1 ECG) and a high incidence of sudden death in patients with structurally normal hearts. An autosomal dominant disease with incomplete penetrance, Brugada syndrome has been linked to mutations in SCN5A, the gene encoding the alpha subunit of the cardiac sodium channel. More than 80 mutations in SCN5A have been linked to this syndrome (references cited in Reference 1). Analysis of several of these mutations has consistently demonstrated a loss of function related to multiple mechanisms, including failure of sodium channel protein expression and changes in the voltage and time dependence of sodium channel current activation, inactivation, or reactivation. Still, SCN5A mutations have been reported in only ≈20% of patients with Brugada syndrome diagnosed on the basis of clinical criteria, suggesting that other genetic defects and/or other disease mechanisms may give rise to this clinical picture. To complicate matters further, SCN5A mutations have also been identified in patients with the long-QT syndrome. These mutations generally lead to a “gain of function” in the sodium channel, which prolongs the QT interval by increasing inward current. In fact, at least 3 human diseases have been linked to defects in this gene: Brugada syndrome, long-QT syndrome, and progressive conduction disturbances. Furthermore, there is considerable overlap of clinical profiles, so some patients with Brugada syndrome also have atrial fibrillation, conduction defects with sinus node abnormalities, or prolonged QT interval (reviewed in Reference 1). Thus, genotype-phenotype relationships in Brugada syndrome are highly complex and serve to underscore our incomplete knowledge of the pathogenesis of this type of inherited arrhythmogenic disease.

A similar area of increasing complexity and uncertainty has to do with the notion that Brugada syndrome occurs in patients with structurally normal hearts. Like the long-QT syndrome, Brugada syndrome is conventionally thought of as a “primary electrical heart disease” arising in myocardium that is otherwise structurally and functionally normal. Nevertheless, it is becoming increasingly recognized that some types of myocardial pathology occur in patients with the clinical picture of Brugada syndrome, even when conventional clinical assessment identifies no obvious features of structural heart disease.

The uncertain and highly complex relationship between the clinical manifestations of Brugada syndrome, the presence of SCN5A gene mutations, and structural heart disease has been brought into sharper focus with the report by Frustaci et al in this issue of Circulation. These investigators studied 18 consecutive patients (15 men and 3 women; mean age, 42 ± 12 years) who exhibited typical ECG features of Brugada syndrome and were judged to have had normal cardiac structure and function on the basis of conventional noninvasive analysis with 2-dimensional echocardiography. Ventricular fibrillation was documented in 7 patients, sustained polymorphic ventricular tachycardia in 7, and syncope in 4 at the time of initial clinical presentation. All patients underwent physical examination and extensive noninvasive evaluation, including 2-dimensional echocardiography, with careful attention paid to right ventricular morphology and function, ergometric testing, and cardiac MRI. Moreover, all patients underwent biventricular endomyocardial biopsies obtained 1 to 3 months after the last known arrhythmic event in an effort to limit the possibility that any observed structural abnormalities might have been caused directly by the arrhythmia. Finally, the entire coding region of the SCN5A gene was analyzed in all patients, and in selected patients, the entire coding regions of the RyR2 (cardiac ryanodine receptor) and the PKP2 (plakophilin-2) genes were also screened.

Remarkably, pathological features were found in endomyocardial biopsies in each of the 18 consecutive patients included in this study. Most of the patients had biopsy evidence of myocarditis. Diffuse or localized right ventricular inflammation was observed in 14 patients (78%), and viral genomes were detectable by polymerase chain reaction in 4 of them (Coxsackie B3 in 2 patients, and Epstein-Barr virus and Parvovirus B-19 in single patients). Interestingly, the typical ST-segment abnormalities in the right precordial leads that formed the basis of the diagnosis of Brugada syndrome disappeared a few weeks after hospital discharge and were not observed again at follow-up in 8 patients in whom endomyocardial biopsy revealed myocardial inflammation and in whom no SCN5A gene mutations were identified. These observations provide further evidence that myocarditis may mimic Brugada syndrome and may account for the

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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transient development of the characteristic ECG abnormalities in some patients.

Other types of cardiac muscle pathology were observed in biopsies from the remaining 4 patients. The right ventricular biopsy in 1 patient showed extensive fibrofatty replacement of cardiac myocytes, the main pathological feature of arrhythmogenic right ventricular cardiomyopathy. Hypertrophy and vacuolization of cardiac myocytes, nonspecific abnormalities consistent with diffuse muscle disease of the sort typically present in dilated cardiomyopathy, were observed in the remaining 3 patients. Of note, the right ventricular biopsy was abnormal in all 18 patients, whereas the left ventricular biopsy was judged to have been normal in 10 patients. This suggests that biventricular biopsy is not necessary and that conventional right ventricular biopsy is the more sensitive approach to identifying structural heart disease in patients with the clinical picture of Brugada syndrome.

Genetic analysis revealed single-base-pair SCN5A mutations in 4 of the 18 patients, a proportion that is consistent with the general reported experience. All 4 were novel mutations, not previously reported, and each led to amino acid substitutions. Expression and functional analysis of these mutations revealed abnormal proteins that formed channels with reduced inward current, similar to the functional defects identified in other mutations linked to Brugada syndrome. Because all patients in this study had biopsy evidence of myocardial pathology, the 4 patients with documented SCN5A mutations and abnormal sodium channel function also had positive biopsies, but none of these patients had myocardiitis on their biopsies. In fact, 3 of the 4 exhibited myocyte hypertrophy and vacuolization. These are entirely nonspecific changes, and it is sometimes difficult to distinguish their presence or to assess the extent of this type of pathology, given the usual amount of artifactual tissue disruption that occurs during the endomyocardial biopsy procedure itself. Nevertheless, these observations add weight to the notion that a primary abnormality in a cardiac ion channel may, itself, lead to cellular damage. Indeed, age-dependent development of myocardial fibrosis and progressive slowing of atrial and ventricular conduction have been reported in mice with a single null allele in the SCN5A gene (SCN5A<sup>−/−</sup> mice). Frustaci et al<sup>5</sup> speculate that deranged intracellular sodium homeostasis caused by an SCN5A mutation could act via sodium-hydrogen and sodium-calcium exchangers to affect intracellular pH and calcium flux, which, in turn, could impair excitation-contraction coupling and energy production. Whatever the mechanism, ongoing structural remodeling of the myocardium in a patient with a mutation in the SCN5A gene could help explain the delayed development of ECG abnormalities and arrhythmias and possibly account for the eventual progression of Brugada syndrome to a state characterized by cardiac dilatation and dysfunction.

The observations reported by Frustaci et al<sup>5</sup> have highlighted the complexities between the clinical manifestations of Brugada syndrome, the presence of SCN5A mutations, and the presence of structural heart disease. Although most patients who present with clinical manifestation of Brugada syndrome may have structurally normal hearts, it also appears that some patients who present with the clinical features of Brugada syndrome may have structural heart disease, which contributes to the expression of the clinical syndrome, with or without SCN5A mutations. These observations led Frustaci et al<sup>5</sup> to propose that the ECG pattern of ST-segment elevation in the right precordial leads should not be regarded as a marker of a specific syndrome but rather a common electrical manifestation of structural abnormalities in the right ventricle that may have genetic, infectious, and/or inflammatory origins.

The idea that patients with the clinical features of Brugada syndrome can have underlying structural abnormalities is not new. In 1996, Corrado et al<sup>7</sup> described a family with autosomal dominant inheritance of clinical features of Brugada syndrome, including ST-segment elevation, right bundle-branch block, and sudden death, but in whom post-mortem investigation disclosed right ventricular dilation, myocardial atrophy, fibrofatty replacement of the right ventricular free wall, and fibrotic disruption of the right bundle branch. These authors concluded that the definitive diagnosis of a functional electrical disease can be supported only when detailed clinical and morphological studies, including autopsy in fatal cases, have ruled out concealed heart muscle disease.

Similar findings were reported by members of this same group in 2001 in a clinicopathological study of 273 young (≤35 years of age) sudden death victims from the Veneto region of Italy. Twelve-lead ECGs were available from 96 subjects, and within this group, 13 (14%; 12 men and 1 woman; age, 24±8 years) exhibited right precordial ST-segment elevation that was associated with right bundle-branch block in 4 cases. At autopsy, 12 of 13 showed pathological features of arrhythmogenic right ventricular cardiomyopathy, and 1 had an apparently normal heart.

Bezzina et al<sup>9</sup> characterized a family in which affected members exhibited irregular wide complex tachycardia and in whom mutational analysis revealed compound heterozygous nonsense and missense mutations in the SCN5A gene. Pathological analysis of the heart in 1 family member revealed changes of dilated cardiomyopathy with severe degenerative abnormalities of the cardiac conduction system. And more recently, Papavassiliou et al<sup>10</sup> evaluated cardiac MRIs in 20 patients with the clinical features of Brugada syndrome. They observed significant enlargement of the right ventricular outflow track in the Brugada syndrome patients compared with control subjects. High intramyocardial T1 signal, suggestive of fat, was observed in 4 patients but in none of the control subjects.

Taken together, these reports have convincingly demonstrated that the clinical features of Brugada syndrome may be associated with structural abnormalities, including those characteristic of arrhythmogenic right ventricular cardiomyopathy and dilated cardiomyopathy, even in patients who harbor mutations in SCN5A. Frustaci et al<sup>5</sup> have built on this foundation and have provided striking new evidence implicating myocardiitis in the transient development of Brugada-like ECG abnormalities and arrhythmias.

Clearly, much more work needs to be done to clarify the mechanistic links between electrical instability in Brugada syndrome and the presence of genetic mutations in SCN5A (and presumably other genes) and to elucidate their complex interrelations with the development of structural heart dis-
ease. For now, it seems likely that some patients who fulfill clinical criteria for Brugada syndrome may have a primary heart muscle disease such as myocarditis that can cause the characteristic ECG features in the absence of an underlying sodium channel defect. It is not known what proportion of the ∼80% of Brugada syndrome patients without SCN5A mutations may fall into this category. Certainly, myocarditis should be considered if, on follow-up, the ECG manifestations and arrhythmias of Brugada syndrome disappear. Conversely, it is also becoming increasingly clear that patients with clinical features of the Brugada syndrome and an underlying SCN5A mutation may also have structural heart disease. It remains to be determined whether the genetic defect itself contributes to the development of structural heart disease or whether the 2 arise independently and, in combination, contribute to the clinical phenotype.

Disclosure
None.

References

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Structural Heart Disease, SCN5A Gene Mutations, and Brugada Syndrome: A Complex Ménage à Trois
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