Cardiac Histological Substrate in Patients With Clinical Phenotype of Brugada Syndrome

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Background—The role of structural heart disease and sodium channel dysfunction in the induction of electrical instability in Brugada syndrome is still debated.

Methods and Results—We studied 18 consecutive patients (15 males, 3 females; mean age 42.0±12.4 years) with clinical phenotype of Brugada syndrome and normal cardiac structure and function on noninvasive examinations. Clinical presentation was ventricular fibrillation in 7 patients, sustained polymorphic ventricular tachycardia in 7, and syncope in 4. All patients underwent cardiac catheterization, coronary and ventricular angiography, biventricular endomyocardial biopsy, and DNA screening of the SCN5A gene. Biopsy samples were processed for histology, electron microscopy, and molecular screening for viral genomes. Microaneurysms were detected in the right ventricle in 7 patients and also in the left ventricle in 4 of them. Histology showed a prevalent or localized right ventricular myocarditis in 14 patients, with detectable viral genomes in 4; right ventricular cardiomyopathy in 1 patient; and cardiomyopathic changes in 3. Genetic studies identified 4 carriers of SCN5A gene mutations that cause in vitro abnormal function of mutant proteins. In these patients, myocyte cytoplasm degeneration was present at histology, whereas terminal dUTP nick end-labeling assay showed a significant increase of apoptotic myocytes in right and left ventricle versus normal controls (P=0.014 and P=0.013, respectively).

Conclusions—Despite an apparently normal heart at noninvasive evaluation, endomyocardial biopsy detected structural alterations in all 18 patients with Brugada syndrome. Mutations in the SCN5A gene, identified in 4 of the 18 patients, may have induced concealed structural abnormalities of myocardiocytes that accounted for paroxysmal arrhythmic manifestations. (Circulation. 2005;112:3680-3687.)

Key Words: death, sudden ■ cardiomyopathy ■ ion channels ■ endomyocardial biopsy ■ myocytes

In 1989, Martini et al1 described the ECG pattern of right bundle-branch block and ST-segment elevation in survivors of cardiac arrest. In 1992, Brugada and Brugada2 identified this ECG pattern as a new distinctive syndrome characterized by augmented risk of sudden death and no demonstrable structural heart disease.

Editorial p 3672

Brugada syndrome (BS) has been defined as an autosomal dominant disease with incomplete penetrance and has been linked to mutations in the SCN5A gene encoding for the alpha-subunit of the cardiac sodium channel.3–4 SCN5A mutations, reported in ~20% of cases, cause a loss of function of the channel that reduces the inward sodium current, thus inducing conduction delay and predisposing the substrate for reentry.

The identification of a genetic defect of the sodium channel associated with the clinical phenotype has further sustained the definition of the syndrome as a functional electrical disorder that does not reflect underlying cardiac abnormalities. Nevertheless, the presence of structural cardiac disease as part of the phenotype of the BS has been suggested repeatedly5 but never demonstrated conclusively. In particular, the occurrence of the typical ECG pattern in patients with arrhythmogenic right ventricular cardiomyopathy reported by the Padua group raises the possibility of a myocardial pathological substrate.6,7 Therefore, it remains unclear whether the ECG and clinical features of BS may be the expression of structural cardiac disease and whether the reported abnormal sodium channel function may be associated with structural changes.

The aim of the present study was to investigate by endomyocardial biopsy whether concealed cardiac abnormalities are present in patients with BS and whether the presence

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of mutation in the SCN5A gene is associated with a structurally normal heart, as previously proposed. Accordingly, we report the biventricular endomyocardial biopsy findings and the correlation with clinical, ECG, and molecular diagnosis of BS; the present results shed new light on the pathophysiology of the disease and may help to account for its paroxysmal arrhythmic manifestations.

Methods

Patient Population
From January 2001 to December 2002, we studied 18 consecutive unrelated probands (15 males and 3 females; mean age 42.0±12.4 years) with clinical and instrumental diagnosis of BS. Eight of these patients were referred to our institution for possible BS because it is a tertiary referral center dedicated to the study of heart muscle diseases, whereas the remaining patients were intrastitutional referrals. Sixteen patients were white, 1 patient was a native of India, and 1 patient was a native of Southeast Asia (the Philippines). According to the most recently proposed diagnostic criteria,8 the clinical presence of BS was based on the demonstration on the ECG of a type 1 (coved) ST-segment elevation in the presence or absence of a channel blocker in more than 1 right precordial lead (V1 to V3), or of a type 1 (coved) ST-segment elevation in the presence or absence of a channel blocker or a type 2 (saddleback) ST-segment elevation that was converted to type 1 after challenge with a sodium channel blocker in more than 1 right precordial lead (V1 to V3), associated with a documented ventricular fibrillation (VF), self-terminating polymorphic ventricular tachycardia (VT), syncpe, or family history (<45 years) of sudden cardiac death. No evidence of systemic disease, drug abuse, and electrolyte imbalance or 2D echocardiography abnormalities of cardiac valves, right and left ventricular dimensions, or contractility at the time of clinical presentation was reported from the referring hospital. At admission, a clinical and family history was collected, and all patients underwent physical examination and noninvasive studies that included 2D echocardiography with assessment of right ventricular morphology and function,4–6 ergometric test, and cardiac MRI. Study protocols were approved by the institutional review boards of our institutions.

Cardiac Catheterization and Endomyocardial Biopsy
After they provided written informed consent, all patients were submitted to cardiac catheterization, coronary angiography with ergonovine test, biplane right and left ventricular angiography (right anterior oblique view 20° and 30°, respectively, and left anterior oblique view 60°), and biventricular endomyocardial biopsy 1 to 3 months after the arrhythmic event. Evaluation of angiographic findings was obtained by 2 independent, experienced hemodynamicians blinded to the clinical data. Abnormal features were considered significant when the interpretation of the 2 cardiologists coincided. Endomyocardial biopsies were performed in the septal-apical region of the left and right ventricle (8 to 10 samples per patient). Myocardial specimens were either fixed in 10% buffered formalin or frozen in liquid nitrogen for histology or frozen in liquid nitrogen for molecular biology studies.

Histology and Immunohistochemistry
Five-micron-thick sections were stained with hematoxylin-eosin, Miller’s elastic Van Gieson, and Masson’s trichrome and examined by light microscopy. Immunohistochemistry for the characterization of inflammatory infiltrates was performed as described previously.9 The diagnosis of myocarditis was established in the presence of inflammatory infiltrates associated with necrosis of adjacent myocytes, according to the Dallas criteria.10 Apoptosis was measured in all SCN5A gene mutation carriers by the TUNEL (terminal deoxyuridine transferase-mediated dUTP nick end-labeling) method with the Apoalert DNA fragmentation assay kit (BD Biosciences) that incorporates fluorescein-dUTP at the free 3′-hydroxyl ends of the fragmented DNA. The results were visualized directly by confocal microscopy. Myocardioocytes were detected by α-sarcomeric actin antibody staining (clone 5C5,Sigma, St Louis, Mo). Nuclei were labeled by propidium iodide. Biventricular biopsy samples from 5 patients undergoing surgical repair of atrial septal defect were used as normal controls for apoptosis assessment. Histological and immunohistochemical analysis were performed by a pathologist blinded to clinical and genetic data.

Screening of Myocardial Specimens for Viral Genome
Polymerase chain reactions (PCR) and reverse transcription-PCR analysis were performed on frozen endomyocardial biopsy samples to assess the presence of cardiotropic viruses (adenovirus, enterovirus, cytomegalovirus, parvovirus B19, influenza A and B viruses, herpes simplex viruses, Epstein-Barr virus, and hepatitis C virus) as described previously.9 Frozen surgical ventricular samples from 50 patients undergoing mitral valve replacement with no evidence of myocarditis at histology were used as controls.

Electrophysiological Studies
An electrophysiological study was performed in all subjects with stimulation in the apex and the outflow tract of the right ventricle at 3 drives (600, 430, and 330 ms) and up to 3 extrastimuli at a minimal coupling interval of 200 ms. The stimulation protocol was interrupted if VF or sustained (>30 seconds) or syncopal polymorphic VT was induced.

Genetic Studies
DNA analysis was performed by investigators blinded to pathology findings. DNA was extracted from peripheral blood lymphocytes. The entire coding region of the SCN5A gene was amplified with primer pairs as described previously.11 Denaturing high-performance liquid chromatography analysis was performed on amplified genomic DNA (Transgenomic). Abnormal patterns were sequenced directly on both strands (ABI Prism 310, Perkin Elmer). A panel of 400 healthy race-matched individuals (800 alleles) was used as control.

In the patient with fatty tissue infiltration, the genes associated with autosomal dominant arrhythmogenic right ventricular cardiomyopathy were also screened. The entire coding region of the RYR2 gene (cardiac ryanodine receptor) was screened by denaturing high-performance liquid chromatography analysis and sequencing, and the coding region of the PKP2 (plakophilin-2) gene was screened by direct sequencing.

Expression of Recombinant Na+ Channels
Na+ channels were expressed in human embryonic kidney (HEK) 293 cells as described previously.12 Briefly, transient transfection was performed with equal amounts of Na+ channel α-subunit cDNA (wild type or mutant) and hβ1-subunit cDNA subcloned into the pcDNA3.1(+)(Invitrogen) vector (total 1 cDNA 2.5 μg). The same amount of CD8 cDNA was cotransfected as reporter gene (ATTC). Expression of channels was studied with patch-clamp procedures 48 hours after transfection.

Electrophysiology
Membrane currents were measured with whole-cell patch-clamp procedures with Axopatch 200B amplifiers (Axon Instruments). All measurements were obtained at room temperature (22°C). Macroscopic whole-cell Na+ current was recorded with previously published solutions and protocols.11 PClamp8 (Axon Instruments), Excel (Microsoft), and Origin 6.1 (Microcal Software) were used for data acquisition and analysis.

Statistical Analysis
Distribution of continuous variables was assessed with Kolmogorov-Smirnov and Shapiro-Wilks test. Continuous variables were expressed as mean±SD if they demonstrated a normal distribution and as median (range) otherwise. Categorical variables were presented as proportion of cases. Means of continuous variables that showed...
normal distribution were compared with the Student t test for independent samples. Continuous variables that did not show a normal distribution were compared with nonparametric statistics (Mann-Whitney test). Comparison of proportions of categorical variables was performed with a χ² test; in the case of an expected cell count of <5, Fisher’s exact test was used. A 2-tailed \( P < 0.05 \) was considered statistically significant. Statistical analysis was performed with SPSS version 11.0.1 software (SPSS Inc).

**Results**

Clinical characteristics of patients are summarized in Table 1. All patients presented an ECG that was diagnostic for BS: 13 patients had a type I (coved) ECG pattern (Figure 1A), and 5 had a type II pattern that evolved into a type I pattern after intravenous administration of flecainide (2 mg/kg body weight, with a maximum of 150 mg in 10 minutes). ECG analysis showed a PQ interval of 167 ± 23 ms, QRS duration of 104 ± 19 ms, and a QTc interval of 407 ± 24 ms. No patient showed epsilon waves, whereas complete right bundle-branch block was present in 3 cases, and left-axis deviation was present in 4 cases; at electrophysiological testing, HV time was 47 ± 7 ms. Clinical arrhythmias were documented in 14 of 18 patients (VF in 7, VT in 7); 4 patients experienced a syncopal event. In 4 cases (patients 2, 9, 10, and 17 in Table 1), arrhythmic events were associated with fever. Plasma electrolytes and troponin I were within normal ranges in all subjects. No patient was taking tricyclic antidepressants or had a history of cocaine abuse. A familial history of sudden cardiac death or nonfatal cardiac arrest was present in 4 patients (patients 1, 12, 17, and 18). In all cases, both echocardiography and cardiac magnetic resonance failed to show significant abnormalities of cardiac chamber dimensions and profile, wall-motion abnormalities, or signal-intensity alterations compatible with fibrofatty replacement, fibrosis, or myocardial edema.

### Cardiac Catheterization and Angiography

No left or right ventricular dysfunction was documented. Augmented left (17.5 ± 3.2 mm Hg) and right (12.2 ± 3.9 mm Hg) ventricular end-diastolic pressure was detected in all patients. Coronary angiography with ergonovine test was negative in all cases. At right ventricular angiography, 7 patients had localized microaneurysms of either the diaphragmatic wall (4 patients; Figure 1B) or the outflow tract (3 patients), with a classic “pile of dishes” pattern in 1 patient (patient 2). Among the 7 patients with microaneurysms of the right ventricle, 4 (patients 7, 8, 10, and 11) showed additional localized microaneurysms, also of the diaphragmatic wall of the left ventricle (Figure 1C; Table 2).

### Histology and Immunohistochemistry

Fourteen patients had a lymphocytic myocarditis with focal necrosis of the adjacent myocytes (Figure 1D); immunohistochemistry showed a prevalence of activated T lymphocytes (CD8+, CD45RO+; Figure 1E). In 6 cases, inflammatory infiltrates were present in both ventricles, whereas in 8 patients, they were observable only in the right ventricle. In 1 patient, right ventricular specimens showed extensive (>30%) fibrofatty myocardial replacement (Figure 2) that was diagnostic for arrhythogenic right ventricular cardiomyopathy. Hypertrophy and diffuse vacuolization of myocytes, with cytoplasm degeneration more pronounced in right ventricular specimens (cardiomyopathic changes), were observed in the last 3 patients (Figure 3A). Remarkably, all 3 patients with cardiomyopathic changes and the patient with fibrofatty myocardial replacement were carriers of a genetic defect in the SCN5A gene (see below). TUNEL assay of biopsy samples from the 4 patients with SCN5A gene mutations revealed more apoptosis (Figure 3; 0.05% or 502 ± 320 per 10⁶ myocyte nuclei in the left ventricle and 0.09% or

<table>
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<tr>
<th>Pt</th>
<th>Age/Sex</th>
<th>Clinical Presentation</th>
<th>Repolarization Pattern</th>
<th>Drug Challenge</th>
<th>SCN5A Mutation</th>
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Pt indicates patient; M, male; and F, female.
958±429 per 10^6 myocyte nuclei in the right ventricle) than in normal controls (0.001% or 10±6 per 10^6 myocyte nuclei in the left ventricle and 0.0008% or 8±5 per 10^6 myocyte nuclei in the right ventricle; P=0.013 and P=0.014, respectively).

Genetic Studies and Functional Characterization of Mutant Proteins
Four novel single base pair mutations leading to an amino acid substitution were identified in the SCN5A gene (Tables 1 and 2). The functional properties of the mutant proteins were compared with the wild type by heterologous expression in HEK 293 cells. We transiently expressed the 4 mutations to look for functional properties that discriminated the mutant channel from the wild type (Table 3) and demonstrated that all mutants result in functionally abnormal proteins. All abnormalities induced in the cardiac sodium channel led to a reduced inward current and were consistent with those previously identified in BS.14 The patient carrier of the R376H mutation in the SCN5A gene who presented histological evidence of fatty tissue infiltration (Tables 1 and 2) presented no mutations in the RyR2 gene or in the PKP2 gene.

Viral Genome in Myocardial Specimens
Viral genome was detected in 4 patients (28%) with myocarditis: coxsackievirus B3 (patients 1 and 7), Epstein-Barr virus (patient 14), and parvovirus B19 (patient 18). None of the controls were positive for any viral genome.

Electrophysiological Studies
Programmed electrical stimulation induced VF in the 7 patients with aborted sudden death. In the 4 patients with syncope, VF (n=2) and polymorphic VT (n=1) were induced. Among the 7 patients with documented sustained polymorphic VT, electrophysiological study was negative in 2 cases and reproduced the spontaneous arrhythmia in 5.

Treatment and Follow-Up
Twelve patients (1 with sustained polymorphic VT, 7 survivors of VF, and 4 patients with syncope) received an implantable cardioverter defibrillator (ICD). All other patients refused the ICD and did not receive any antiarrhythmic treatment (Table 2). Patients were followed up by physical examination, resting ECG, Holter monitoring, 2D echocardiography, and cardioversion.
ography, and ICD arrhythmic event retrieval, monthly in the first 6 months and every 3 months thereafter.

At a mean follow-up of 25.5 ± 6.2 months (range 17 to 39 months), ICD interrogation revealed the occurrence of sustained monomorphic VT episodes effectively terminated by the ICD in the patient with arrhythmogenic right ventricular cardiomyopathy, whereas no major arrhythmic events were observed in any of the other patients (Table 2). Cardiac function remained normal in all patients. At ECG, ST-segment elevation was detected at all follow-up visits in 10 patients (including 4 of 4 SCN5A mutation carriers), whereas it was no longer observed in 8 patients with myocarditis. In 5 cases, the ST segment normalized suddenly in the first 6 months, whereas in the remaining 3 patients, it normalized through a transient phase characterized by normal ST segment with negative T waves in the right precordial leads (V1 through V3).

### Discussion

Brugada syndrome is a leading cause of life-threatening arrhythmias and juvenile sudden cardiac death. It is a genetic disease caused by mutation of the SCN5A gene encoding for the α-subunit of the cardiac sodium channel. However, SCN5A mutations are detected in ∼20% of patients with the clinical phenotype of BS, which suggests that various myocardial entities result in the same clinical picture, likely with a different impact on both prognosis and treatment. Actual criteria for the definition of BS recommend the exclusion of specific myocardial diseases, particularly arrhythmogenic right ventricular cardiomyopathy and myocarditis, before a conclusive diagnosis is reached. Noninvasive techniques including echocardiography and cardiac magnetic resonance are often unable to identify the initial phase or the focal variant of these entities or the presence of cardiac microaneurysms. Invasive cardiac studies, including coronary and biventricular angiography with endomyocardial biopsy, may provide relevant diagnostic contributions but rarely are applied systematically in patients with a clinical phenotype of BS. In particular, biventricular endomyocardial biopsy with extensive sampling associated with immunohistochemistry.

### TABLE 2. Angiographic, Pathological, and Genetic Features, Treatment, and Follow-Up of Study Population

<table>
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<tr>
<th>Pt</th>
<th>RV and LV Angiography</th>
<th>RV Histology†</th>
<th>LV Histology</th>
<th>SCN5A Mutation</th>
<th>Treatment</th>
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RV indicates right ventricle; LV, left ventricle; RVA, right ventricular aneurysms; LVA, left ventricular aneurysms; CM, cardiomyopathic changes; A, asymptomatic; and VT, sustained ventricular tachycardia.

Figure 2. Right ventricular endomyocardial biopsy from patient 2, a carrier of an SCN5A gene mutation (R376H), which at histology showed extensive myocardial fibrofatty infiltration typical of arrhythmogenic right ventricular cardiomyopathy. Hematoxylin and eosin; original magnification ×250.
and molecular and genetic studies has never been performed before and may be of crucial importance if the clinical picture would be sustained by a specific potentially treatable disease.

In the present study, angiography identified ventricular morphological abnormalities in 7 of 18 patients, whereas at histology, structural changes were observed in all cases, including those with mutations of SCN5A gene. These data are a sharp departure from the current view that BS is a functional disease devoid of structural abnormalities. The high prevalence of abnormal histological findings in the present study can be explained by the extensive use of biventricular endomyocardial biopsy and by the number of diagnostic procedures applied to the biopsy samples. In particular, it has been revealed that the use of immunohistochemistry can improve the diagnosis of myocarditis from 8% to 38%. Finally, our results are in accordance with the reported postmortem evidence of remarkable histological changes in BS patients who had a previous normal endomyocardial biopsy and with the recent observation of dilated cardiomyopathy associated with some SCN5A gene mutations.

Endomyocardial Biopsy Findings in Patients With BS and No SCN5A Gene Mutations

Specific morphological changes were observed in the 14 patients who did not have SCN5A gene mutations, which consisted of lymphocytic myocarditis with documented viral genome in 4 patients and which were associated with right ventricular microaneurysms in 5. Consistent with the hypothesis that BS is mainly a disease of the right ventricle, myocarditis was always localized or more pronounced in the right ventricular myocardium. In accordance with the inflammatory origin of this condition mimicking the BS, in 8 patients, the typical ST-segment elevation in the right precordial leads disappeared a few weeks after discharge from hospital and was never again observed at follow-up.

The knowledge that myocarditis may mimic the BS is not novel; nevertheless, the present study indicates that it can be recognized in as much as 77% of an unselected population that presents with the clinical phenotype of BS and sustained

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**Figure 3.** Right ventricular endomyocardial biopsy from patient 12, a carrier of an SCN5A gene mutation (R1644C), which at histology (A) showed hypertrophy and vacuolization of myocytes (arrows). In the same patient, TUNEL assay (B) showed DNA strand breaks (apoptosis; green fluorescent dots) of a myocyte nucleus (arrow). Nuclei were labeled by propidium iodide (blue fluorescence). Myocyte cytoplasm is recognized by the red fluorescence of α-sarcomeric actin. A, Hematoxylin and eosin; original magnification ×250. B, Original magnification ×400; bar represents 10 μm.

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**TABLE 3. Functional Characterization of SCN5A Mutant Proteins**

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Current Density, pA/pF</th>
<th>Sustained Current</th>
<th>Voltage Dependence of Activation, mV</th>
<th>Steady State Inactivation, mV</th>
<th>Onset of Inactivation at −40 mV, ms</th>
<th>Recovery From Inactivation, ms</th>
</tr>
</thead>
<tbody>
<tr>
<td>WT</td>
<td>−319.5±17</td>
<td>Absent</td>
<td>$V_{1/2} = -43.5 ± 0.3$ k=6.2±0.1</td>
<td>$V_{1/2} = -65.6 ± 0.7$ k=5.1±0.1</td>
<td>$t_0 = 1.7 ± 0.8$</td>
<td>$t_0 = 3.9 ± 0.2$</td>
</tr>
<tr>
<td>R376H</td>
<td>−23.1±3.6 (P=0.0001)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>R1023H</td>
<td>−268±28 (P=0.03)</td>
<td>Absent</td>
<td>$V_{1/2} = -40.1 ± 0.1$ k=6.6±0.1</td>
<td>$V_{1/2} = -63.1 ± 1.4$ k=5.1±0.1</td>
<td>$t_0 = 2.9 ± 0.3$ (P=0.002)</td>
<td>$t_0 = 2.7 ± 0.2$</td>
</tr>
<tr>
<td>R1644C</td>
<td>−401±44 (P=0.002)</td>
<td>Absent</td>
<td>$V_{1/2} = -35.0 ± 0.3$ k=8.6±0.3</td>
<td>$V_{1/2} = -66.6 ± 0.9$ k=5.7±0.1</td>
<td>$t_0 = 1.5 ± 0.2$ (P=0.0006)</td>
<td>$t_0 = 1.8 ± 0.1$</td>
</tr>
<tr>
<td>I1968S</td>
<td>−209.7±31 (P=0.004)</td>
<td>Absent</td>
<td>$V_{1/2} = -43.5 ± 0.2$ k=6.1±0.2</td>
<td>$V_{1/2} = -65.9 ± 1.2$ k=5.2±0.1</td>
<td>$t_0 = 0.9 ± 0.07$ (P=0.0002)</td>
<td>$t_0 = 2.1 ± 0.2$</td>
</tr>
</tbody>
</table>

WT indicates wild type; NA, not available. All values are presented as mean±SD; P values refer to comparison of each mutation vs wild type.

The major reduction in current density obtained with the R367H mutation did not allow further characterization of current kinetics.
ventricular arrhythmias. This observation may have therapeutic implications, because selective treatment may be indicated in case the disease progresses to cardiac dilation and dysfunction.

**Endomyocardial Biopsy Findings in Patients With BS and SCN5A Gene Mutations**

Even the 4 BS patient carriers of a mutation in the SCN5A gene that was shown by functional studies to cause derangement in the sodium inward current presented structural abnormalities, which consisted of hypertrophy with cytoplasm degeneration of myocytes. These findings were obtained 1 to 3 months from the arrhythmic presentation, which rules out the possibility that they could be the result of the arrhythmia itself or a consequence of defibrillation.

These data confirm in patients with a clinical phenotype of BS that an abnormality in a cardiac ion channel may lead to cell damage and death; although we cannot prove that these patients are not carriers of mutations in other genes that cause structural diseases, we consider this unlikely. With regard to the possible mechanisms that link sodium channel loss of function to cellular damage, it is well established that intracellular sodium homeostasis has a relevant role in myocellular function, because through the action of sodium-hydrogen and sodium-calcium exchangers, it may influence the regulation of both intracellular pH and calcium homeostasis, thus impairing excitation-contraction coupling and energy production mechanisms. On this basis, it can be argued that the arrhythmic event may occur when a sufficient degree of cell damage has been reached owing to the severity of ion channel protein mutation. This would explain why, in the context of an inborn defect, several years might elapse before the arrhythmic manifestation of the disease or why in some patients the severity of cell damage might induce morphological-functional abnormalities and even progression of the disease to cardiac dilation and dysfunction. In this regard, it has been shown that mutations in the SCN4A gene, the homologous skeletal muscle sodium channel gene, may lead to muscle weakness and progressive degenerative myopathy. Moreover, in genetically engineered mice, deficiency in voltage-gated sodium channels has been demonstrated to cause apoptosis and neuronal cell death. Interestingly, apoptosis is a pathogenetic mechanism demonstrated in the heart of patients with arrhythmogenic right ventricular cardiomyopathy and that is consistent with the finding that 1 of the patients investigated in the present study, who had mutations in the cardiac sodium channel gene, also had right ventricular aneurysms and fatty tissue infiltration at histology. In the BS patients with SCN5A mutations in the present study, myocyte apoptosis in both the left and right ventricular myocardium was significantly higher than in controls. Myocyte loss due to apoptotic cell death, together with impaired intracellular homeostasis, may explain the macroscopic alterations observed in 2 of the patients in the present study and the recent reports of dilated cardiomyopathy associated with some SCN5A gene mutations. The identification of fatty tissue replacement and a BS-like ECG confirms previous reports that suggest that fatty tissue replacement in the right ventricle may be a histological substrate of BS.

**Conclusions**

We provide evidence that patients with the ECG pattern of BS despite an apparently normal heart at clinical and noninvasive investigation have concealed structural abnormalities that are localized mainly in the right ventricle. The heterogeneity of the histological findings suggests that environmental factors such as viral infection and inflammation may create myocardial cell damage that may induce an ECG pattern consistent with the diagnosis of BS. We also confirmed previous reports that in a minority of patients with the typical ECG pattern of BS, fatty tissue replacement may be observed. Finally, SCN5A mutations were identified in 18% of patients, in agreement with previous data; interestingly, carriers of SCN5A mutations demonstrated myocardial cell degeneration and death. In conclusion, these data suggest that as shown in other tissues, abnormalities in the function of sodium channels may induce structural abnormalities and cell death. On the basis of the present observations, we propose that the ECG pattern of ST-segment elevation in the right precordial leads is not a marker of a specific syndrome; rather, it is a common electrical manifestation of structural abnormalities in the right ventricle that may have genetic, infective, and inflammatory origins.

**Acknowledgments**

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**Disclosures**

None.

**References**


Cardiac Histological Substrate in Patients With Clinical Phenotype of Brugada Syndrome
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