Electrocardiographic Characteristics and SCN5A Mutations in Idiopathic Ventricular Fibrillation Associated With Early Repolarization

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Background—Recently, we and others reported that early repolarization (J wave) is associated with idiopathic ventricular fibrillation. However, its clinical and genetic characteristics are unclear.

Methods and Results—This study included 50 patients (44 men; age, 45±17 years) with idiopathic ventricular fibrillation associated with early repolarization, and 250 age- and sex-matched healthy controls. All of the patients had experienced arrhythmia events, and 8 (16%) had a family history of sudden death. Ventricular fibrillation was inducible by programmed electric stimulation in 15 of 29 patients (52%). The heart rate was slower and the PR interval and QRS duration were longer in patients with idiopathic ventricular fibrillation than in controls. We identified nonsynonymous variants in SCN5A (resulting in A226D, L846R, and R367H) in 3 unrelated patients. These variants occur at residues that are highly conserved across mammals. His-ventricular interval was prolonged in all of the patients carrying an SCN5A mutation. Sodium channel blocker challenge resulted in an augmentation of early repolarization or development of ventricular fibrillation in all of 3 patients, but none was diagnosed with Brugada syndrome. In heterologous expression studies, all of the mutant channels failed to generate any currents. Immunostaining revealed a trafficking defect in A226D channels and normal trafficking in R367H and L846R channels.

Conclusions—We found reductions in heart rate and cardiac conduction and loss-of-function mutations in SCN5A in patients with idiopathic ventricular fibrillation associated with early repolarization. These findings support the hypothesis that decreased sodium current enhances ventricular fibrillation susceptibility. (Circ Arrhythm Electrophysiol. 2011;4:874-881.)

Key Words: arrhythmia ■ sodium channel ■ electrophysiology ■ genetics ■ mutations

Clinical Perspective on p 881

Early repolarization or J-wave is characterized by an elevation at the junction between the end of the QRS complex and the beginning of the ST-segment (J-point) in a 12-lead ECG and generally has been considered benign for decades. However, early repolarization can be observed under various negative biological conditions, such as low body temperature and ischemia, and there is increasing evidence that early repolarization is associated with an increased risk of ventricular fibrillation and sudden cardiac death.
In previous studies, including our own, early repolarization in the inferior or lateral leads was associated with pathogenesis in idiopathic ventricular fibrillation.5,6 Moreover, early repolarization in the right precordial leads also has been associated with idiopathic ventricular fibrillation.8 Heritability of early repolarization has been shown in a recent population-based study,9 and as in other arrhythmia syndromes such as long QT syndrome and Brugada syndrome,10 ion channel genes are responsible for idiopathic ventricular fibrillation associated with early repolarization.11–13 A mutation in KCNJ8, which encodes a pore-forming subunit of the ATP-sensitive potassium channel, has been identified in idiopathic ventricular fibrillation with early repolarization.11,14 Mutations in L-type calcium channel genes, including CACNA1C, CACNB2B, and CACNA2D1, also have been associated with idiopathic ventricular fibrillation with early repolarization.12

In this study, we compared electrocardiographic parameters between patients with idiopathic ventricular fibrillation and healthy controls and found that heart rate and cardiac conduction were slow in patients with idiopathic ventricular fibrillation. Furthermore, we screened patients with idiopathic ventricular fibrillation for mutations in SCN5A, which encodes the predominant cardiac sodium channel α subunit and is critical for cardiac conduction. Here, we present the clinical and in vitro electrophysiological characteristics in idiopathic ventricular fibrillation associated with early repolarization.

Methods

Study Populations

This study included patients with idiopathic ventricular fibrillation and early repolarization who were referred to our institutions. Patients were diagnosed with idiopathic ventricular fibrillation if they had no structural heart disease as identified using echocardiography, coronary angiography, and left ventriculography. Baseline electrophysiological studies without antiarrhythmic drugs were performed based on the indication of each institution. Early repolarization was defined as an elevation of the J-point, either as QRS slurring or notching ≥0.1 mV ≥2 consecutive leads in the 12-lead ECG.5 Patients were excluded if they had a short QT interval (corrected QT interval using Bazett formula <340 ms) or a long QT interval (corrected QT interval >440 ms) in the 12-lead ECG.15,16 All patients received sodium channel blocker challenge, and patients with Brugada type ST-segment elevations at baseline or after sodium channel blocker challenge were excluded.17 Twelve-lead electrocardiograms recorded in the absence of antiarrhythmic drugs were compared between patients with idiopathic ventricular fibrillation and control subjects who were matched to patients with idiopathic ventricular fibrillation based on gender and age (patient: control ratio, 1:5). Control subjects were selected from 86 068 consecutive electrocardiograms stored in the ECG database in Niigata University Medical and Dental Hospital from May 7, 2003 to July 2, 2009.18 Control subjects who had a normal QT interval (corrected QT interval, 360 to 440 ms) and no cardiovascular disease or medication use were included. Control subjects with Brugada type ST-segment elevations or early repolarization were excluded.

Genetic Analysis

All probands and family members who participated in the study gave written informed consent before genetic and clinical investigations in accordance with the standards of the Declaration of Helsinki and local ethics committees. Genetic analysis was performed on genomic DNA extracted from peripheral white blood cells using standard methods. The coding regions of KCNQ1, KCNH2, SCN5A, KCNE1, and KCNE2, and KCNJ8 were amplified by PCR using exon-flanking intronic primers,19–21 and direct DNA sequencing was performed using ABI 310, 3130, and 3730 genetic analyzers (Applied Biosystems, Foster City, CA).22

Generation of Expression Vectors and Transfection in Mammalian Cell Lines

Full-length human SCN5A cDNA was subcloned into the mammalian expression plasmid pcDNA3.1+ (Invitrogen, Carlsbad, CA).23 Mutant constructs were prepared using a QuickChange site-directed mutagenesis kit (Stratagene, La Jolla, CA) according to the manufacturer’s instructions. The human cell line tsA201 was transiently transfected with wild-type or mutant SCN5A plasmid using Lipo-lectamine LTX (Invitrogen), in combination with a bicistronic plasmid (pcDNA-IRE5-hβ1) encoding CD8 and the human sodium channel β1 subunit (hβ1) to visually identify cells expressing heterologous hβ1 using Dynabeads M-450 CD8 (Invitrogen).24 Electrophysiological measurements were performed 24 to 72 hours after transfection.

Electrophysiology

Sodium currents were recorded using the whole-cell patch clamp technique as previously described.25 Electrode resistance ranged from 0.8 to 1.5 mol/L. Data were acquired using an Axopatch 200B patch clamp amplifier and pCLAMP8 software (Axon Instruments). Sodium currents were filtered at 5 kHz (~3 dB, 4-pole Bessel filter) and were digitally sampled at 50 kHz using an analog-to-digital interface (Digidata 1322A; Molecular Devices, Sunnyvale, CA). Experiments were performed at room temperature (20 to 22°C). Voltage errors were minimized using series resistance compensation (generally 80%). Cancellation of the capacitance transients and leak subtraction were performed using an online I/I4 protocol. The time from establishing the whole-cell configuration to the onset of recording was consistent (5 minutes) between cells to exclude possible time-dependent shifts of steady-state inactivation. The pulse protocol cycle time was 10 s. The data were analyzed using Clampfit 10 (Molecular Devices) and SigmaPlot 9 software (Aspire Software International, Ashburn, VA). The holding potential was ~120 mV. The bath solution contained the following (in mmol/L): 145 NaCl, 4 KCl, 1.8 CaCl2, 1 MgCl2, 10 HEPES, and 10 glucose, pH 7.35 (adjusted with NaOH). The pipette solution (intracellular solution) contained the following (in mmol/L): 10 NaF, 110 CsCl, 20 CsCl, 10 EGTA, and 10 HEPES, pH 7.35 (adjusted with CsOH).

Immunocytochemistry

For immunocytochemistry, the FLAG epitope was inserted between residues 153 and 154 of the extracellular linker S1-S2 in domain I. The FLAG insertion into the S1-S2 linker previously has been shown to have no effect on channel gating or cell surface expression.22,23 Immunocytochemistry was performed in HEK293 cells transfected with wild-type or mutant SCN5A plasmid as described previously.23 After 48 hours of transfection, the cells were washed with phosphate-buffered saline, fixed in 4% paraformaldehyde, and permeabilized with 0.15% Triton X-100 in phosphate-buffered saline with 3% bovine serum albumin. Then the cells were stained with anti-FLAG polyclonal antibody (F7425; Sigma-Aldrich, St Louis, MO; 1:100) for 1 hour at room temperature. Protein reacting with antibody was visualized with Alexa Fluor 568–labeled secondary antibody (A-11011, Invitrogen, 1:1000). Images were collected using a Zeiss LSM 510 laser confocal microscope and analyzed using LSM 4.0 software.

Data Analysis

Differences in parameters between patients with idiopathic ventricular fibrillation and control subjects were analyzed using conditional logistic regression models. To exclude the effects of multicollinearity among electrocardiographic parameters, each electrocar-
idiopathic ventricular fibrillation showed type I Brugada ventricular fibrillation than control subjects. No patient with idiopathic fibrillation compared with control subjects. The corrected QT interval were longer in patients with idiopathic ventricular fibrillation (Table 1). The heart rate was slower, and the PR interval and QT interval.

Results

We identified 50 patients with idiopathic ventricular fibrillation and early repolarization (44 men [88%]; mean age, 45 ± 17 years). All of the patients had experienced arrhythmia events, and 8 (16%) had a family history of sudden death.

Electrocardiographic parameters were compared between 50 patients with idiopathic ventricular fibrillation and 250 healthy control subjects without cardiovascular disease and not taking medication who were matched with gender and age (Table 1). The heart rate was slower, and the PR interval and QRS duration were longer in patients with idiopathic ventricular fibrillation compared with control subjects. The corrected QT interval was shorter in patients with idiopathic ventricular fibrillation than control subjects. No patient with idiopathic ventricular fibrillation showed type I Brugada electrocardiograms in repeated recordings. Sodium channel blockers were administered in all patients, and Brugada type electrocardiograms were not provoked in any of these patients. Electrophysiological study was performed in 29 patients. His-ventricular interval was 48 ± 9 ms, and 4 patients had prolonged His-ventricular time ≥ 55 ms. Ventricular fibrillation was inducible by programmed electric stimulation in 15 patients (52%).

We screened for mutations in SCN5A in 26 unrelated patients with idiopathic ventricular fibrillation and identified 3 mutations (A226D, R367H, and L846R) in 3 patients (Figure 1, Table 2). R367H and L846R are predicted to be located in the pore region. These mutations were not found in the genomes of 200 healthy control individuals. Two of the patients exhibited prolongation of the PR interval, and sodium channel blocker challenge was negative for Brugada syndrome in all of them. Alignment of the amino acid sequences from multiple species demonstrated that the amino acids substituted by mutations are highly conserved, supporting the importance of these amino acids. A226D and L846R, but not R367H, are predicted to change the electric charge of substituted amino acids.

A missense mutation, A226D (Figure 1A), was identified in a 36-year-old man (patient 1) resuscitated from ventricular fibrillation. He had experienced multiple episodes of syncope. The physical examination and echocardiography were normal. His ECG showed prolongation of the PR interval and early repolarization in leads II, III, and aVF, and J-point/ST-segment elevation in lead V1 (Figure 2A). Administration of pilsicainide augmented early repolarization in the inferior leads and induced ventricular fibrillation, but did not produce a type I Brugada ECG in the right precordial leads (Figure 2B). Electrophysiological study revealed prolongation of His-ventricular interval (68 ms), and ventricular fibrillation was induced by programmed electric stimulation. The patient’s family history was negative for syncpe, sudden cardiac death, and epilepsy.

A missense mutation L846R (Figure 1B) was identified in a 27-year-old man (patient 2). He was admitted after multiple episodes of syncope, and polymorphic ventricular tachycardia was documented when he lost consciousness. The physical examination and echocardiography were normal. His ECG

Table 1. Electrocardiographic Parameters

<table>
<thead>
<tr>
<th></th>
<th>NF Patients</th>
<th>Controls</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex, N (%)</td>
<td>44 (88)</td>
<td>220 (88)</td>
<td>. . .</td>
<td>. . .</td>
</tr>
<tr>
<td>Age, y</td>
<td>45 ± 17</td>
<td>45 ± 16</td>
<td>. . .</td>
<td>. . .</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>62 ± 9</td>
<td>70 ± 14</td>
<td>0.62 (0.47–0.81)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>PR interval, ms</td>
<td>175 ± 34</td>
<td>147 ± 20</td>
<td>1.32 (1.22–1.43)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>QRS interval, ms</td>
<td>96 ± 14</td>
<td>89 ± 8</td>
<td>1.63 (1.31–2.02)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>QTc, ms</td>
<td>388 ± 25</td>
<td>397 ± 22</td>
<td>0.85 (0.75–0.98)</td>
<td>0.02</td>
</tr>
</tbody>
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NF indicates idiopathic ventricular fibrillation; OR, odds ratio; QTc, corrected QT interval.
showed prolongation of the PR interval and early repolarization in lead III (Figure 2C). During the recovery phase of exercise testing, the amplitude of the J-point/ST-segment was augmented in leads I, II, III, and aVF, and ventricular fibrillation was induced. Pilsicainide caused marked prolongation of QRS duration and augmented the J-point/ST-segment amplitude in leads V1 and V2, followed by the development of ventricular fibrillation (Figure 2C and 2D). Pilsicainide did not produce a type I Brugada ECG. During electrophysiological study, His-ventricular interval was 55 ms. His uncle died suddenly.

We previously reported a missense mutation R367H in patient 3 as a case with Brugada syndrome (Figure 1C). However, idiopathic ventricular fibrillation associated with early repolarization was diagnosed at a later time because a type 1 Brugada ECG has never been seen spontaneously or after the administration of sodium channel blocker in more than 1 right precordial lead, and thus the diagnostic criteria for Brugada syndrome were not fulfilled. When the patient admitted to the hospital after recurrent episodes of syncope, early repolarization was present in the inferior and right precordial leads (Figure 2E). After sinus pause, early repolarization was augmented in leads II, III, and aVF, followed by the development of ventricular fibrillation after a few hours of the admission (Figure 2F). Procainamide further exaggerated early repolarization but did not produce a type I

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Sex</th>
<th>Age at Onset (y)</th>
<th>Family History of SCD</th>
<th>Presenting Symptom</th>
<th>Location of J Wave</th>
<th>Other ECG Abnormalities</th>
<th>Response to Sodium Channel Blocker</th>
<th>Amino Acid Substitution</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>36</td>
<td>N</td>
<td>Aborted SCD</td>
<td>II, III, aVF, V1</td>
<td>PR prolongation</td>
<td>Augmentation of J-point amplitude and VF</td>
<td>A226D</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>27</td>
<td>Y</td>
<td>Aborted SCD</td>
<td>I, II, III, aVF</td>
<td>PR prolongation</td>
<td>Marked QRS prolongation and VF</td>
<td>L846R</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>37</td>
<td>N</td>
<td>Aborted SCD</td>
<td>II, III, aVF, V2</td>
<td>N</td>
<td>Augmentation of J-point amplitude and marked QRS prolongation</td>
<td>R367H</td>
</tr>
</tbody>
</table>

ECG indicates electrocardiogram; SCD, sudden cardiac death.
Brugada ECG (Figure 2G). During electrophysiological study, His-ventricular time was prolonged (65 ms) and ventricular fibrillation was not induced. The patient’s family history was negative for syncope, sudden cardiac death, and epilepsy.

The electrophysiological characteristics of the mutant sodium channels were assessed in transfected mammalian cells using the whole-cell patch-clamp technique. Figure 3 shows representative current traces in cells expressing wild-type or mutant SCN5A channels. There was no detectable current in A226D, R367H,27 and L846R mutant channels. Immunostaining revealed that cells expressing A226D channels showed cytoplasmic fluorescence, while cells expressing wild-type channels showed marked peripheral fluorescence, suggesting that the mutation results in trafficking defect (Figure 4). Cells expressing R367H channels and those expressing L846R channels showed a similar fluorescence pattern to wild-type channels, suggesting that these mutations do not affect trafficking.

**Discussion**

In this study, patients with idiopathic ventricular fibrillation associated with early repolarization exhibited slower heart rate and slower cardiac conduction properties than did controls. We found rare, nonsynonymous variants in SCN5A in patients who had idiopathic ventricular fibrillation associated with early repolarization. These variants affect highly conserved residues, and all of the mutant SCN5A channels failed to generate any currents when expressed in heterologous expression systems. Immunostaining experiments suggested 2 possible mechanisms for the sodium channel dysfunction by the SCN5A mutations, a defect of channel trafficking to cell surface in A226D and critical alterations of the structures required for the sodium ion permeation or gating in R367H and L846R that are predicted to be located at the pore region.

Loss-of-function mutations in SCN5A are associated with a wide range of inherited arrhythmia syndromes, including Brugada syndrome, progressive cardiac conduction disease, and sick sinus syndrome.28–30 Furthermore, our results suggest that SCN5A is a causative gene of idiopathic ventricular fibrillation associated with early repolarization. Evidence supporting disease causality of the mutations includes the identification of 3 mutations in 3 unrelated probands who shared similar clinical phenotypes and the loss of sodium channel function effects in heterologous expression systems in all of the mutant channels.

Although our findings suggest that loss of sodium channel function plays a role in idiopathic ventricular fibrillation associated with early repolarization, the mechanisms of early repolarization are not understood well. In wedge preparations of canine ventricles, early repolarization results from increased action potential notches at the ventricular epicardium by either a decrease in inward currents or an increase in outward currents.31 A mutation in KCNJ8, which encodes the ATP-sensitive potassium channel, recently has been identified in idiopathic ventricular fibrillation associated with early repolarization.11 The KCNJ8 mutation has shown gain-of-function effects in ATP-sensitive potassium channels in heterologous expression studies,14 and augmentation of ATP-sensitive potassium currents results in the development of ventricular fibrillation in wedge preparations.32 Decreased calcium currents also have been proposed as a mechanism for idiopathic ventricular fibrillation associated with early repolarization.33 Mutations in L-type calcium channel genes, including CACNA1C, CACNB2B, and CACNA2D1, recently have been identified; however, functional studies are not yet available.12 Our findings that mutant SCN5A channels displayed loss of sodium channel function, resulting in a decrease of inward currents, are consistent with findings in prior studies and with the proposed mechanism.11,12,14,33
In this study, heart rate and cardiac conduction were slower in patients with idiopathic ventricular fibrillation than in healthy controls. Furthermore, His-ventricular interval was prolonged in all of the patients carrying an SCN5A mutation. Reductions in heart rate and conduction may result from underlying electrophysiological abnormalities in idiopathic ventricular fibrillation. In addition to the maintenance of the action potential dome, normal impulse generation and propagation are dependent critically on normal sodium channel function, and reductions in heart rate and conduction we observed here can be partially explained by loss-of-function mutations in SCN5A. Viskin et al initially reported the association of short QT interval with idiopathic ventricular fibrillation, and the recent study also showed that corrected QT interval is shorter in idiopathic ventricular fibrillation patients with early repolarization than those without early repolarization. In this study, corrected QT interval was shorter in patients with idiopathic ventricular fibrillation than in healthy controls, in line with the previous findings. Furthermore, we have previously reported that early repolarization is frequently found in patients with short QT syndrome. There may be the association between short QT interval and early repolarization, although the mechanism is unknown.

Idiopathic ventricular fibrillation associated with early repolarization and Brugada syndrome characterized by J-point/ST-segment elevation in the right precordial leads share genetic, clinical, and pharmacological characteristics. Rare variants in genes encoding L-type calcium channel and ATP-sensitive potassium channel have been associated with both diseases. Defects in SCN5A are responsible for Brugada syndrome, and we found that mutations in SCN5A were possible causative genetic factors in idiopathic ventricular fibrillation associated with early repolarization. Furthermore, an R367H SCN5A mutation identified in this study also has been reported in a family affected by Brugada syndrome. However, the mechanism by which loss of sodium channel function results in either Brugada syndrome or idiopathic ventricular fibrillation associated with early repolarization is unknown, similar to that in other arrhythmia phenotypes caused by loss of function mutations in SCN5A, the so called cardiac sodium channelopathies. There may be other genetic or environmental factors that modify the clinical phenotype. Although the association of inferolateral early repolarization with idiopathic ventricular fibrillation has been initially reported, early repolarization in the right precordial leads, where Brugada type electrocardiograms can be seen, also has been associated with idiopathic ventricular fibrillation. In this study, 2 of the 3 patients carrying an SCN5A mutation showed J-point elevation in the right precordial leads, but did not show diagnostic Brugada type ST-segment elevations in multiple ECG recordings even after sodium channel blocker challenge. Sinus node dysfunction and conduction disorders often are seen in Brugada syndrome, and we observed similar electrocardiographic characteristics in idiopathic ventricular fibrillation. Bradycardia-dependent augmentation of J-point amplitude has been reported in both diseases and we observed similar changes of J-wave in a patient carrying SCN5A mutation. The recent studies have shown that early repolarization is found in 14 to 24% of patients with Brugada syndrome, and that early repolarization is associated with the increased risk of arrhythmia events, although the role of early repolarization in Brugada syndrome is not clear. The electrocardiographic manifestations of Brugada syndrome may be unmasked or augmented by sodium channel blockers. In our present and prior studies, the administration of sodium channel blockers resulted in the augmentation of J-point amplitude or development of ventricular fibrillation in patients with idiopathic ventricular fibrillation. The efficacy of isoproterenol and quinidine also is common in both diseases.

In conclusion, we have shown reductions in heart rate and cardiac conduction in patients with idiopathic ventricular fibrillation associated with early repolarization. We identified SCN5A mutations in patients with idiopathic ventricular fibrillation and showed that mutant channels did not generate any currents. These findings implicate that SCN5A is a disease gene for idiopathic ventricular fibrillation associated with early repolarization, and that it plays a role in the electrocardiographic characteristics of idiopathic ventricular fibrillation, at least in part.

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1061–1070.


CLINICAL PERSPECTIVE

Idiopathic ventricular fibrillation associated with early repolarization is a new arrhythmia syndrome entity, although early repolarization has been considered benign for decades. Early repolarization is a heritable electrocardiographic phenotype and there is a positive family history in 10 to 20% of patients with idiopathic ventricular fibrillation associated with early repolarization. Recent studies have identified the causative genes of the arrhythmia, all of which are associated also with Brugada syndrome. In this study, SCN5A, which encodes the predominant cardiac sodium channel subunit and is critical for cardiac conduction, was screened in patients with idiopathic ventricular fibrillation associated with early repolarization. The screening identified 3 patients carrying an SCN5A mutation, and His-ventricular interval was prolonged in all patients. All of the mutations are predicted to substitute amino acids highly conserved across species and failed to produce any detectable sodium current. To identify electrophysiological characteristics in idiopathic ventricular fibrillation associated with early repolarization, we compared electrocardiograms between patients with the arrhythmia and healthy controls. We found that patients with the arrhythmia exhibited slower heart rate and slower cardiac conduction properties than controls. Our findings suggest that there are underlying electrophysiological abnormalities resulting in slow heart rate, slow cardiac conduction, early repolarization, and ventricular fibrillation, partially explained by sodium channel dysfunction. Idiopathic ventricular fibrillation associated with early repolarization and Brugada syndrome share genetic, clinical, and pharmacological characteristics, but other factors that modify the clinical phenotypes are unknown. Further studies to identify the modifiers are warranted.
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