

least in part, contribute to the exercise-induced augmentation in HRV in healthy rats.

APPENDIX: TRANSFER FUNCTION ANALYSIS

The dynamic transfer function from binary white noise stimulation to the HR response was estimated based on the following procedure. Input-output data pairs of the stimulation frequency and HR were resampled at 10 Hz to be consistent with our previous study (21). Subsequently, data pairs were partitioned into eight 50% overlapping segments consisting of 1,024 data points each. For each segment, the linear trend was subtracted and a Hanning window was applied. A fast Fourier transform was then performed to obtain the frequency spectra of nerve stimulation $[N(f)]$ and HR $[HR(f)]$. Over the eight segments, the power of the nerve stimulation $[S_{N-N}(f)]$, the power of the HR $[S_{HR-HR}(f)]$, and the cross-power between these two signals $[S_{N-HR}(f)]$ were ensemble averaged. Finally, the transfer function $[H(f)]$ from nerve stimulation to the HR response was determined using the following equation (20).

$$H(f) = \frac{S_{N-HR}(f)}{S_{N-N}(f)}$$

To quantify the linear dependence of the HR response on vagal or sympathetic stimulation, the magnitude-squared coherence function $[Coh(f)]$ was estimated employing the following equation (20).

$$Coh(f) = \frac{|S_{N-HR}(f)|^2}{S_{N-N}(f) \cdot S_{HR-HR}(f)}$$

Coherence values range from zero to unity. Unity coherence indicates perfect linear dependence between the input and output signals; in contrast, zero coherence indicates total independence between the two signals.

Since the transfer function from sympathetic stimulation to HR response in rats approximated a second order low-pass filter with pure delay (21), we determined the parameters of the sympathetic transfer function using the following equation.

$$H(f) = \frac{K}{1 + 2\zeta \frac{f}{f_N} j + \left(\frac{f}{f_N}\right)^2} e^{-2\pi f j L}$$

where K is dynamic gain (in beats·min⁻¹·Hz⁻¹), f_N is the natural frequency (in Hz), ζ is the damping ratio, L is lag time (in s), and f and j represent frequency and imaginary units, respectively. These parameters were estimated by means of an iterative nonlinear least squares regression.

Since the transfer function from vagal stimulation to HR response in rats approximated a first-order, low-pass filter with pure delay (21), we determined the parameters of the vagal transfer function using the following equation.

$$H(f) = \frac{-K}{1 + \frac{f}{f_C} j} e^{-2\pi f j L}$$

where K represents the dynamic gain (in beats·min⁻¹·Hz⁻¹), f_C denotes the corner frequency (in Hz), L denotes the lag time (in s), and f and j represent frequency and imaginary units, respectively. The negative sign in the numerator indicates the negative HR response to vagal stimulation. These parameters were estimated by means of an iterative nonlinear least squares regression.

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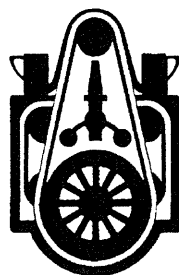
DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

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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

Early repolarization or J-wave is characterized by an elevation at the junction between the end of the QRS

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complex and the beginning of the ST-segment (J-point) in a 12-lead ECG and generally has been considered benign for

decades.¹ However, early repolarization can be observed under various negative biological conditions, such as low body temperature and ischemia,²⁻⁴ and there is increasing evidence that early repolarization is associated with an increased risk of ventricular fibrillation and sudden cardiac death.⁵⁻⁷

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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*, *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).²² Mutant constructs were prepared using a QuikChange 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 Lipofectamine LTX (Invitrogen), in combination with a bicistronic plasmid (pCD8-IRES-h β 1) encoding CD8 and the human sodium channel β 1 subunit (h β 1) to visually identify cells expressing heterologous h β 1 using Dynabeads M-450 CD8 (Invitrogen).²² 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.²² Electrode resistance ranged from 0.8 to 1.5 mol/L Ω . 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 P/4 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 CsF, 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.^{22,24} 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-

Table 1. Electrocardiographic Parameters

	IVF Patients N=50	Controls N=250	OR (95% CI)/ 10 Unit Increase	P Value
Male sex, N (%)	44 (88)	220 (88)
Age, y	45±17	45±16
Heart rate, beats/min	62±9	70±14	0.62 (0.47–0.81)	<0.001
PR interval, ms	175±34	147±20	1.32 (1.22–1.43)	<0.001
QRS interval, ms	96±14	89±8	1.63 (1.31–2.02)	<0.001
QTc, ms	388±25	397±22	0.85 (0.75–0.98)	0.02

IVF indicates idiopathic ventricular fibrillation; OR, odds ratio; QTc, corrected QT interval.

diographic parameter was separately tested in the logistic models. All statistical analyses were performed with SPSS, version 12.0 (SPSS Inc, Chicago, IL). A 2-sided $P < 0.05$ was considered statistically significant. Values are expressed as mean±SD. The study protocol was approved by the ethics committee of each institution.

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.²⁵ Sodium channel blockers were administered in all patients, and Brugada type electrocardiograms were not provoked in any of these patients.²⁵ Electrophysiological study was performed in 29

patients. His-ventricular interval was 48±9 ms, and 4 patients had prolonged His-ventricular time ≥55 ms.²⁶ 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 syncope, 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

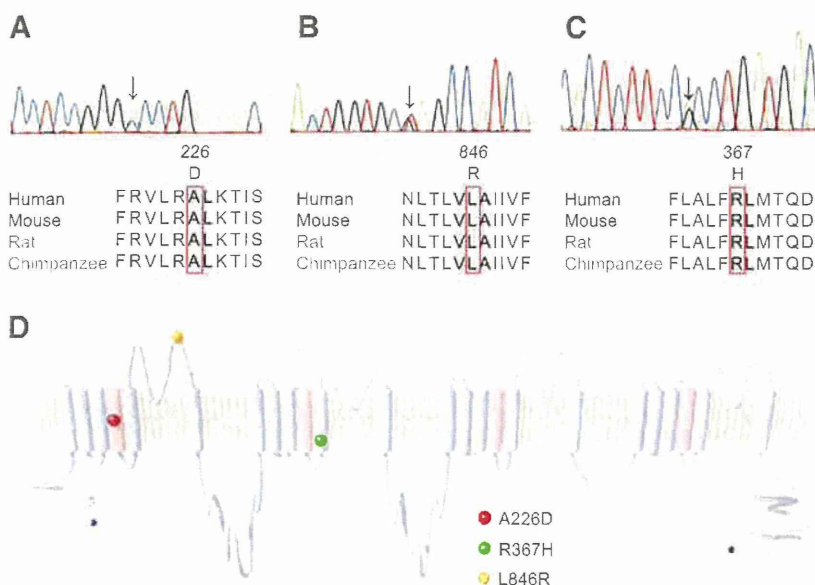


Figure 1. Mutations in *SCN5A* identified in patients with idiopathic ventricular fibrillation associated with early repolarization. **A**, The c.677C→A mutation in *SCN5A* resulting in p.A226D found in patient 1. **B**, The c.2537T→G mutation in *SCN5A*, resulting in p.L846R found in patient 2. **C**, The c.1100G→A mutation in *SCN5A*, resulting in p.R367H found in patient 3. We previously reported the R367H mutation (modified from Takehara et al²⁷). **D**, Predictive topology of the *SCN5A* channel. Circles indicate the locations of the mutations.

Table 2. Characteristics of Idiopathic Ventricular Fibrillation Patients With *SCN5A* Mutations

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

ECG indicates electrocardiogram; SCD, sudden cardiac death.

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).²⁷

However, idiopathic ventricular fibrillation associated with early repolarization was diagnosed at a later time because a type I 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.²⁵ 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

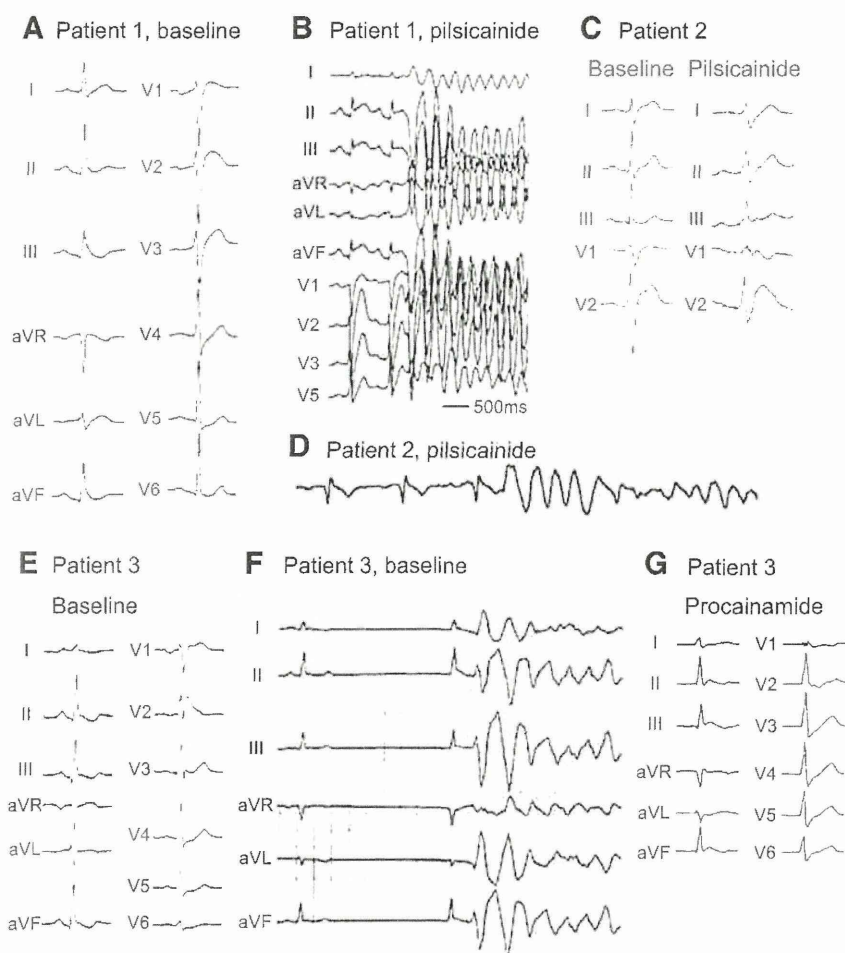


Figure 2. Electrocardiograms of patients with idiopathic ventricular fibrillation and a mutation in *SCN5A*. **A**, Early repolarization was present in the inferior and right precordial leads in patient 1. **B**, After administration of pilsicainide, early repolarization was augmented and ventricular fibrillation developed. **C** and **D**, Pilsicainide caused marked prolongation of QRS duration and J-point elevation in the right precordial leads, followed by the development of ventricular fibrillation in patient 2. **E**, Early repolarization was present in the inferior leads and right precordial leads in patient 3. **F**, The augmentation of early repolarization after sinus pause, followed by ventricular fibrillation. **G**, After the administration of procainamide, early repolarization was augmented in the inferior. In all patients, sodium channel blockers did not provoke a type I Brugada ECG. **E**, **F**, and **G** were modified from Takehara et al.²⁷

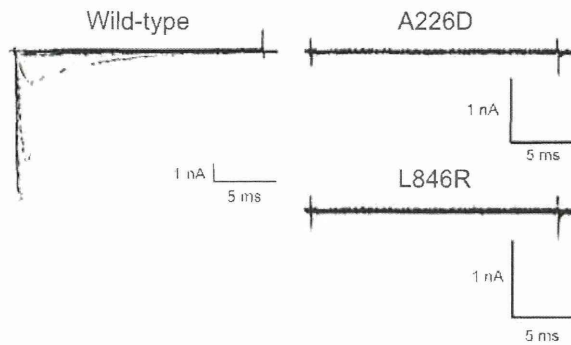


Figure 3. Electrophysiological characteristics of the *SCN5A* mutants. Representative traces of sodium current demonstrating that all of the mutant channels failed to generate any currents. We previously reported that R367H mutant fails to generate any currents.²⁷

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

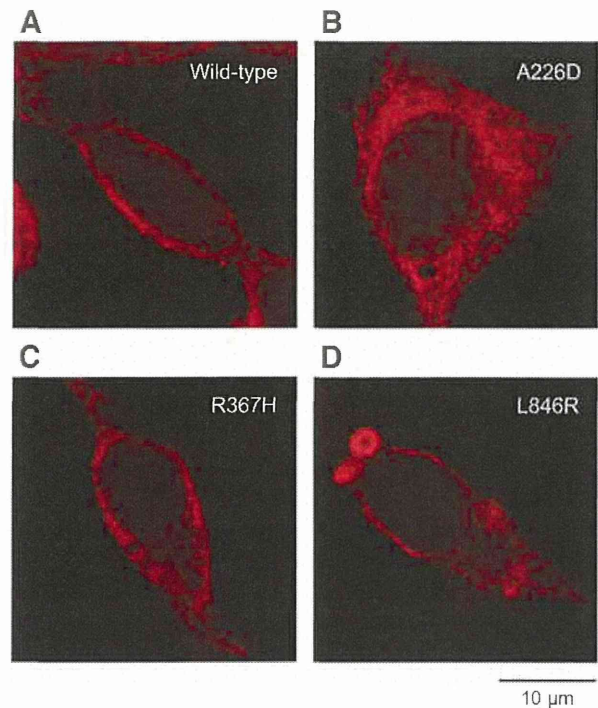


Figure 4. Representative confocal microscopy images. **A**, Cells expressing wild-type *SCN5A* channels showed marked peripheral fluorescence. **B**, Cells expressing A226D channels showed cytoplasmic fluorescence. **C** and **D**, Cells expressing R367H channels and those expressing L846R channels showed a similar fluorescence pattern to wild-type channels.

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,³⁴ 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,³⁵ 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.⁵ In this study, corrected QT interval was shorter in patients with idiopathic ventricular fibrillation than in healthy controls, in line with the previous findings.^{5,35} Furthermore, we have previously reported that early repolarization is frequently found in patients with short QT syndrome.¹⁸ 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.^{5,8,12,17,25,33,36–41} Rare variants in genes encoding L-type calcium channel and ATP-sensitive potassium channel have been associated with both diseases.^{12,14,36} 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.³⁷ 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.⁴² 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,⁵ early repolarization in the right precordial leads, where Brugada type electrocardiograms can be seen, also has been associated with idiopathic ventricular fibrillation.^{8,25} 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.^{17,25} 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.^{43,44} 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,^{12,45} 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.^{17,25} 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.⁴⁶ The efficacy of isoproterenol and quinidine also is common in both diseases.^{8,17,25,38–41}

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.

Acknowledgments

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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 α 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.

Cardiac resynchronization therapy to prevent life-threatening arrhythmias in patients with congestive heart failure

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Abstract

Various clinical data demonstrate that cardiac resynchronization therapy (CRT) provides a favorable structural as well as electrical remodeling. The CARDiac Resynchronization–Heart Failure study, which tested the pure effect of CRT (using CRT devices without the capability of defibrillation) clearly showed a significant reduction in the total mortality by partly preventing sudden cardiac death. The antiarrhythmic effects of CRT are explained, at least in part, by ionic and genetic modulation of ventricular myocytes. It has been revealed in animal experiments to mimic disorganized ventricular contraction that CRT reverses down-regulation of certain K⁺ channels and abnormal Ca²⁺ homeostasis in the failing heart. However, CRT can be proarrhythmic in some particular cases especially in the early phase of this therapy. According to our study, proarrhythmic effects after CRT can be observed in approximately 10% of patients. The relatively high incidence of the proarrhythmic effects of CRT may promote a trend toward selecting CRT-D rather than CRT-P. © 2011 Elsevier Inc. All rights reserved.

Keywords:

Cardiac resynchronization therapy; Ventricular tachyarrhythmia; Heart failure; Proarrhythmic effect; Antiarrhythmic effect

Introduction

Various clinical data demonstrate that cardiac resynchronization therapy (CRT) provides a favorable structural as well as electrical remodeling.^{1–5} The CARDiac Resynchronization–Heart Failure (CARE-HF) study, which tested the pure effect of CRT (using CRT devices without the capability of defibrillation) clearly showed a significant reduction in the total mortality by partly preventing sudden cardiac death (SCD).^{5,6} The antiarrhythmic effects of CRT are attributable to reversal of structural and electrical remodeling of the left ventricle (LV) in association of heart failure toward the creation of substrates for reentry of excitation.

However, epicardial LV pacing can also be proarrhythmic through an induction of heterogeneous ventricular depolarization and repolarization resulting from nonphysiological propagation of excitation.^{7–9} In the present article, we

discuss such a dual potential of CRT toward prevention and promotion of arrhythmias.

Proarrhythmic effects of CRT

Fig. 1 shows a representative case in whom the proarrhythmic effects of CRT were highly suspected. This patient had a long history (>20 years) of heart failure and complete left bundle branch block (CLBBB) without any significant ventricular arrhythmias. The first VF episode developed only 6 days after implantation of CRT-P, giving us a warning against a proarrhythmic risk of CRT even in patients without history of serious ventricular arrhythmias.

Our study

We investigated “early development of lethal arrhythmic events after CRT.”¹⁰ The condition of patients enrolled was defined as follows: (1) no previous episodes of sustained VT/VF or syncope before the CRT implantation, (2) new development of sustained VT/VF, SCD, or appropriate shocks delivered by a CRT-D within 6 months after implantation of CRT. Fifty-one consecutive patients

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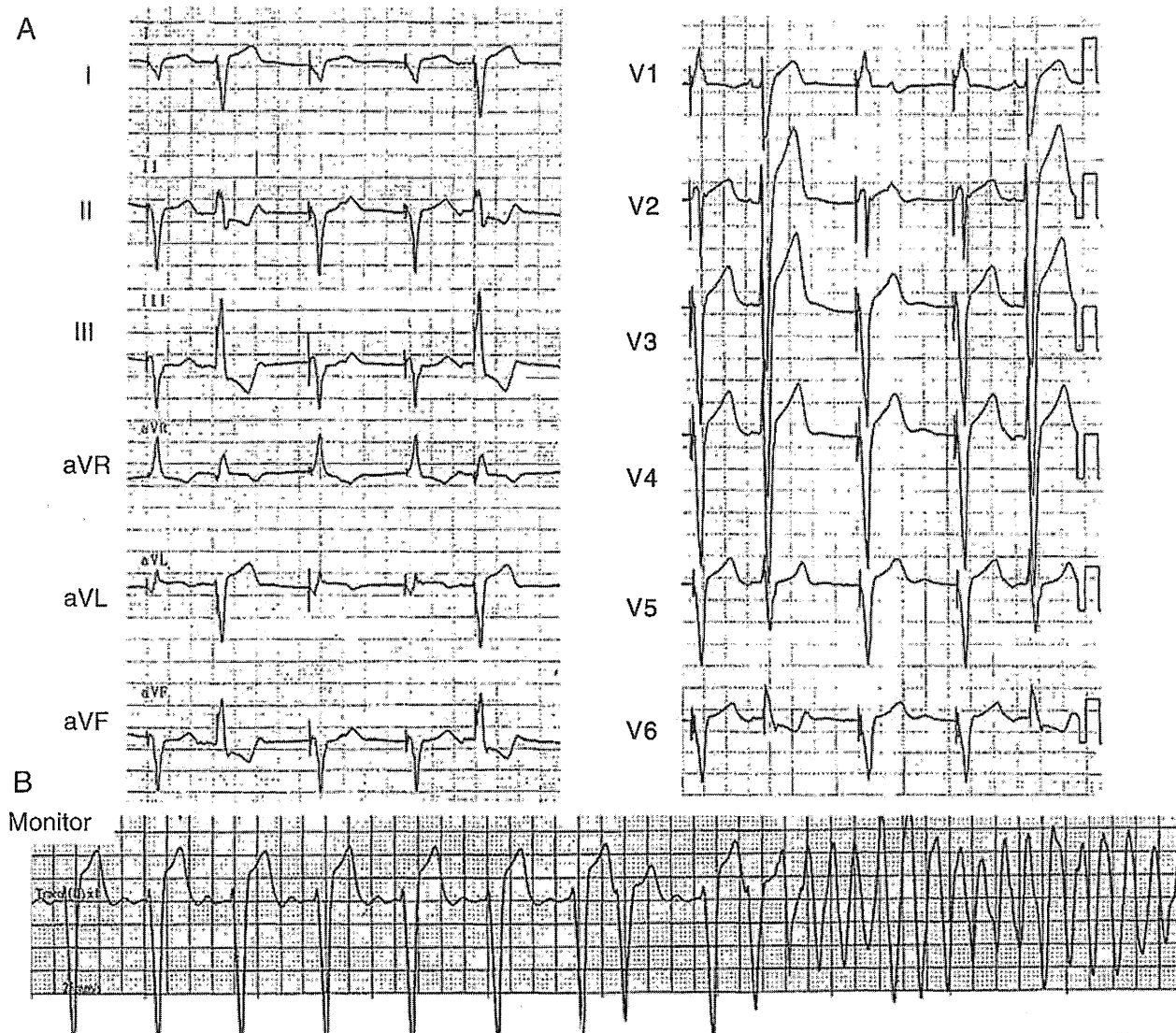


Fig. 1. A case with newly development of VF 6 days after implantation of CRT pacemaker (CRT-P). A, CRT-P was implanted in heart failure patient with CLBBB and permanent AF. Because of AF, occasional conducted QRS complexes with CLBBB configuration are seen. B, This patient had a long history (>20 years) of heart failure and CLBBB without any significant ventricular arrhythmias. The patient showed the first VF episode only 6 days after implantation of CRT-P, giving us a warning against a proarrhythmic risk of CRT.

who underwent CRT were included in this study. We excluded the patients who had a worse New York Heart Association (NYHA) functional class after the CRT and who had VT episodes that were terminated only by antitachycardia pacing. The early development of lethal arrhythmic events after the CRT was observed in 6 (11.7%) of 51 patients. They were divided into 2 groups according to the presence of early phase events: a group with events (group E, $n = 6$) and a group without events (group non-E, $n = 45$), and we compared several clinical parameters such as the baseline NYHA functional class, response to CRT (responder or nonresponder), underlying heart disease, antiarrhythmic drug usage, and preexisting arrhythmias (atrial fibrillation [AF] and nonsustained VT [NSVT]) between the 2 groups. There was no significant difference between the 2 groups for all the parameters except for preexisting arrhythmias. Preexisting AF and NSVT of 5 bursts or more were observed more frequently

in group E than group non-E (6/6 vs 20/45, $P < .01$ and 6/6 vs 17/45, $P < .01$, respectively, Fig. 2). These observations suggest that preexisting AF and NSVT may be important predictors for the proarrhythmic risk of CRT implantation regardless of the hemodynamic response of the subjects.

Mechanism of the proarrhythmic effects of CRT

The transvenous insertion of an LV lead into a cardiac vein on the epicardial surface of the heart is an essential technique to obtain safe and stable long-term LV pacing.¹¹ This technique produces nonphysiological propagation of the excitation from the epicardium to endocardium and may lead to an increase in the dispersion of the repolarization because the epicardial ventricular muscle having shorter action potential duration (APD) is excited earlier than the endocardial ventricular muscle having longer APD. This

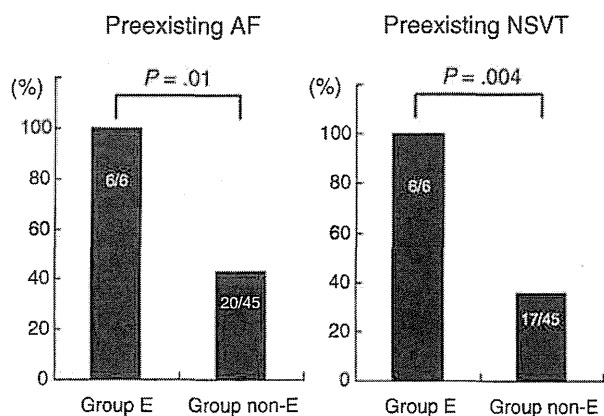


Fig. 2. Preexisting arrhythmias in the patients with (group E) and those without (group non-E) early development of lethal arrhythmic events after CRT. Preexisting AF and NSVT were observed more frequently in group E than group non-E (6/6 vs 19/45, $P < .01$, and 6/6 vs 17/45, $P < .01$, respectively).

may set a stage for reentry of excitation causing VT/VF. Spatially heterogeneous prolongation of APD in the ventricle of failing hearts may further facilitate the initiation and perpetuation of reentrant arrhythmias.^{12,13}

Right ventricular (RV) pacing induces a significant LBBB pattern and sometimes leads to the deterioration in the LV function. Upgrading from a traditional RV pacemaker to a biventricular (Bi-V) pacemaker is highly recommended for patients with a reduced cardiac function and atrioventricular (AV) block (block).¹⁴

Recently, an intriguing case of idiopathic dilated cardiomyopathy with heart failure and complete AV block was reported by Ikutomi et al,¹⁵ where upgrading from the preexisting VDD pacemaker to CRT-D resulted in a significant proarrhythmia. Upgrading from the preexisting VDD pacemaker to CRT-D was performed aiming to improve the heart failure. A marked QT prolongation and torsade de pointes (TdP) occurred immediately after switching from RV pacing to LV or Bi-V pacing. Several weeks later, however, Bi-V pacing caused only moderate QT prolongation without TdP induction. The Bi-V pacing was able to be continued thereafter, and QT interval shortened gradually in association with improvement of heart failure. It is suggested from this report that proarrhythmic risk of Bi-V pacing is most remarkable in the early phase of CRT, and it may decrease in the remote phase probably through a reversal of (or adaptation to) the electrical remodeling of the heart.

Another mechanism of proarrhythmia with CRT is relevant to preexisting anatomical structure in favor of reentry. We experienced a case of nonischemic dilated cardiomyopathy (65 year old man) with heart failure, complete AV block and permanent AF. ICD had been implanted for the treatment of monomorphic sustained VT. During a 3-year follow-up period, the patient experienced sporadic electrical therapies, but his heart failure condition deteriorated gradually to NYHA III/IV. We, therefore, decided to upgrade from ICD to CRT-D. A CRT-D was implanted through thoracotomy. He responded well to CRT-

D, giving rise to an improvement of NYHA class from III/IV to II. One month later, however, he was admitted in the emergency department of our hospital because of frequent episodes of sustained monomorphic VT (an electrical storm). The VT was terminated repeatedly by antitachycardia pacing (Fig. 3A). There were no other factors of proarrhythmia (such as worsening of heart failure or electrolyte imbalance) than Bi-V pacing. After switching from Bi-V to RV pacing, the electrical storm terminated immediately (Fig. 3B). When the pacing turned back to Bi-V pacing, the electrical storm reappeared right away (Fig. 3B). The proarrhythmia of Bi-V pacing in this patient could be explained by an entrance of wave front from LV pacing site into preexisting reentry circuits. Anisotropic fiber orientation in the LV myocardium or summation of depolarizing waves is considered to be involved in such events favoring the electrical storm.^{16,17}

Future device

Advanced technology using transseptal (transmitral) lead approach will provide safe and stable endocardial LV pacing in near future.¹⁸ This technique will resolve proarrhythmic issues of epicardial approach by producing more physiological propagation of depolarization through LV, and it will also allow us to implant the LV lead regardless of cardiac vein anatomy.

Antiarrhythmic effects of CRT

CRT is expected to prevent life-threatening ventricular arrhythmias in the failing heart because the procedure would cause a reversal of structural and electrical remodeling, favoring reentry of excitation.¹⁻⁷ Tanabe et al¹⁹ reported the apparent antiarrhythmic effect of CRT in a patient with idiopathic dilated cardiomyopathy who experienced an electrical storm (frequent monomorphic sustained VT) after implantation of ICD. They performed an acute study with Bi-V pacing before the CRT-D implantation and confirmed an immediate improvement in the systemic hypotension and degree of mitral regurgitation during the Bi-V pacing. Application of CRT to this patient resulted in an immediate hemodynamic improvement in association with complete elimination of the electrical storm, which had been resistant to pharmacological therapies.

An analysis of the combined InSync-ICD and Contact-CD patients demonstrated that CRT was associated with no significant change in the incidence of polymorphic VT or monomorphic VT.²⁰ However, other reports showed data revealing that the incidence of malignant VT was reduced following CRT.^{19,21-23} Based on these results, CRT has favorable or at least no harmful effects on substrates for VT/VF in heart failure patients.

As previously mentioned, the CARE-HF study demonstrated a significant improvement in the SCD rate.⁶ However, in that trial, the survival curves showing the freedom from all causes of death in the control and CRT group began to separate approximately 200 days after the randomization. On the other hand, the survival curves of SCD started to separate after approximately 700 days. The

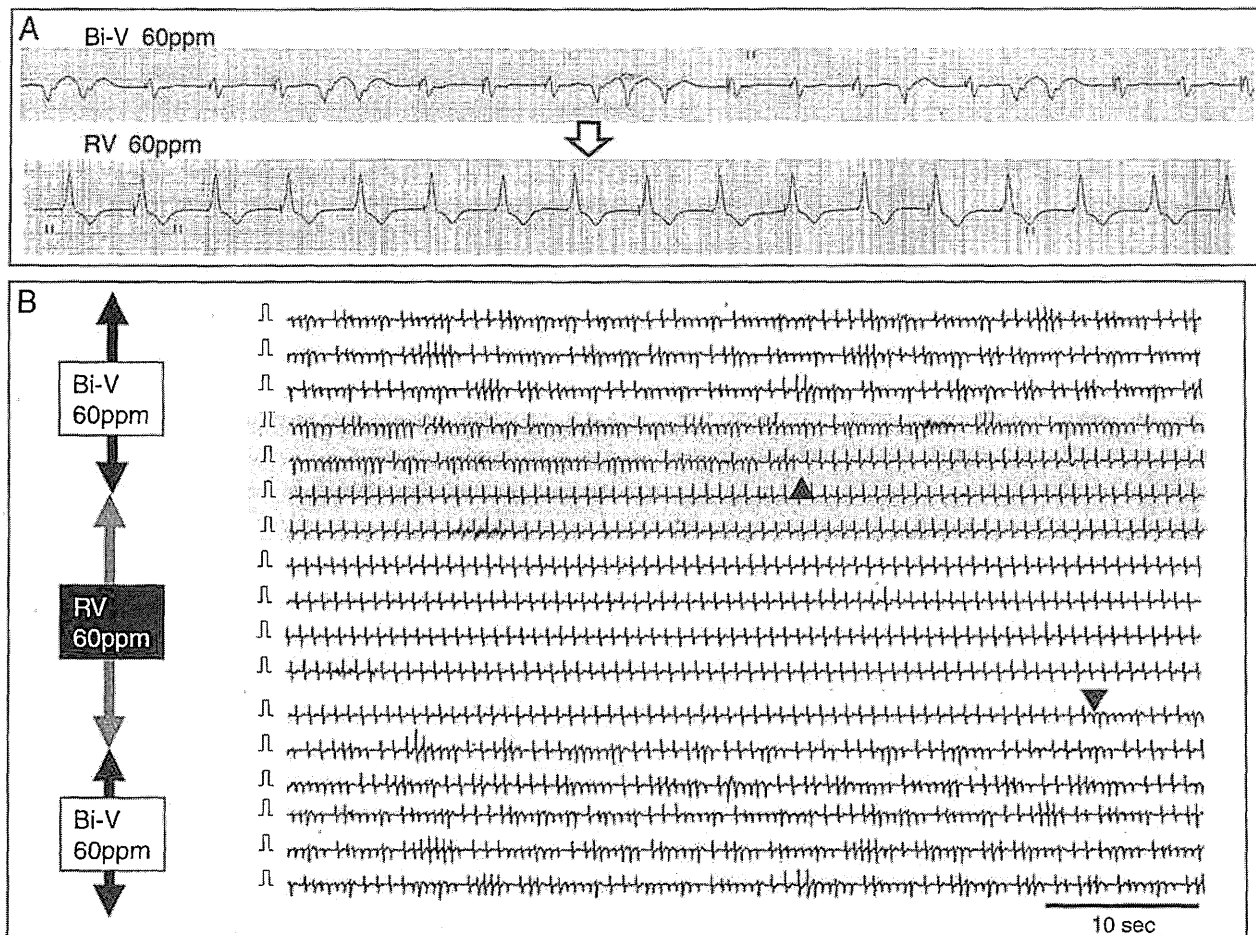


Fig. 3. Proarrhythmic effects of CRT in a patient of dilated cardiomyopathy (65-year-old man) with heart failure, complete AV block, and permanent AF. ICD had been implanted for the treatment of monomorphic sustained VT. Because of deterioration of heart failure, we upgraded from ICD to CRT-D. He responded well to CRT, giving rise to improvement of NYHA classes. One month later, however, he was experienced frequent episodes of sustained monomorphic VT, which were terminated repeated by antitachycardia pacing (A). After switching from Bi-V to RV pacing, the electrical storm terminated immediately (B, upward arrowhead). When the pacing turned back to Bi-V, the electrical storm reappeared right away (B, downward arrowhead). ppm indicates pacing per minute, RV, right ventricular pacing.

antiarrhythmic effect of CRT to prevent SCD might require sufficient time for reversal of structural and electrical remodeling of the heart, although this interpretation remains to be substantiated.

Effects on AF

The incidence of AF increases with an advancing NYHA cardiac functional class.^{24,25} The contribution of the atrial contraction to the cardiac performance in a normal heart is considered to be small. However, the development of AF in a failing heart significantly affects the cardiac dysfunction by diminishing the atrial kick (AV synchrony). Inappropriate rapid ventricular rate with irregular R-R intervals may also contribute the cardiac dysfunction.²⁶⁻²⁸

Optimization of the left AV conduction delay and a simultaneous contraction of the entire LV reduces the LV end-diastolic pressure, leading to a reduction of wall stress in the LV and LA in favor of termination and prevention of AF. We experienced 2 cases in whom long-lasting AF was terminated and sinus rhythm has been maintained thereafter.

Because we did not expect the termination of the AF after the CRT, we did not implant an atrial lead. In cases with unexpected restoration of sinus rhythm as in this patient, Bi-V pacing with the VVI mode may provoke pacemaker syndrome. We need to lean certain parameters predicting conversion from AF to sinus rhythm after CRT implantation.

Delnoy et al²⁹ reported their experience in 96 CRT patients with permanent or persistent AF. They implanted atrial leads in patients with AF lasting less than 2 years and followed them up for 2 years. Antiarrhythmic drug therapy (mainly amiodarone) was used after CRT implantation to resume or to preserve sinus rhythm. In that study, 25% of 96 AF patients were in sinus rhythm after 1 year. Eight patients received cardioversion at the time of the implant, whereas 16 patients reverted to sinus rhythm spontaneously. At 2 years, 21% of the AF group was in sinus rhythm. This study suggests that amiodarone treatment after cardioversion is promising in CRT patients with AF for resumption and preservation of sinus rhythm. They recommended that the implantation of an atrial lead may have merit in CRT patients with AF lasting less than 2 years. AV synchrony obtained by an atrial lead may dramatically improve the

heart failure, but in the case of those without a lead, reversion to sinus rhythm may provoke pacemaker syndrome and an insufficient improvement.

Genetic aspects of reverse electrical remodeling

The electrophysiologic hallmark of cells and tissue isolated from failing hearts is the prolongation of the APD and a conduction delay.^{30,31} In human studies and a number of animal models of heart failure, functional down-regulation of K^+ currents and alterations in depolarizing Na^+ and Ca^{2+} currents and transporters are demonstrated. In experiments on dog of heart failure induced by dyssynchronous LV contraction (DHF), Aiba et al¹² and Aiba and Tomaselli¹³ have shown that CRT partially restores DHF-induced ion channel remodeling and abnormal Ca^{2+} homeostasis and attenuates the regional heterogeneity of APD. CRT was also shown to improve β -adrenergic responsiveness of Ca^{2+} handling in the DHF model. Such electrophysiological changes induced by CRT may suppress ventricular arrhythmias favoring a better survival.³²

Conclusions

CRT can be proarrhythmic in some particular cases especially in the early phase of this therapy until electrical reverse remodeling has become established. According to our study, proarrhythmic effects after CRT can be observed in approximately 10% of patients. The relatively high incidence of the proarrhythmic effects of CRT may promote a trend toward selecting CRT-D rather than CRT-P.

Indeed, CRT can be antiarrhythmic. Even in the early phase after beginning CRT, it immediately improves the hemodynamic situation. A decrease of the LV endodiastolic pressure would ameliorate the stretch-induced arrhythmogenic alterations of ionic currents. In patients who ideally respond to CRT, it creates structural reverse remodeling accompanied by electrical reverse remodeling in the remote phase. Once such a striking reverse remodeling has been established, CRT acts as a potent antiarrhythmic treatment thereafter.

The antiarrhythmic effects of CRT have come to be explained by the viewpoint of the ionic and genetic regulation of the myocytes.

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□ CASE REPORT □

Incessant Monomorphic Ventricular Tachycardia Induced by the Proarrhythmic Effect of Amiodarone

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Abstract

This case report describes incessant monomorphic ventricular tachycardia (VT), not Torsade de Pointes, induced by intravenous amiodarone in a 48-year-old woman with dilated cardiomyopathy. VT was reproducibly triggered by short coupled premature ventricular complex (PVC) with different morphology from VT. After amiodarone infusion, the coupling interval of initiating PVC was prolonged, and moreover, the morphology of initiating PVC became the same as that of VT. Though amiodarone has become the first line drug to treat ventricular tachyarrhythmias in patients with cardiac dysfunction, it is important to be aware of its proarrhythmic effect, which may lead to an electrical storm of monomorphic VT.

Key words: monomorphic ventricular tachycardia, amiodarone, proarrhythmia, Torsade de Pointes, class III antiarrhythmic

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Introduction

Ventricular tachycardia/fibrillation (VT/VF) is one of the major causes of death in patients with structural heart disease. Amiodarone, which is classified as a class-III antiarrhythmic agent, is considered as the most efficacious agent even for patients with severe cardiac dysfunction (1). Amiodarone has been broadly used in the emergency department of outpatient clinics, and it is also well known that the electrophysiological effect of amiodarone is different when it is administered orally or intravenously (2). Although proarrhythmic effects of amiodarone are rare, some patients occasionally develop polymorphic VT of Torsade de Pointes (TdP) (3, 4). We present an unusual case with incessant monomorphic VT, not TdP, induced after amiodarone infusion.

Case Report

A 48-year-old woman was admitted to our hospital due to

sudden palpitation, and dyspnea. She had been diagnosed as idiopathic dilated cardiomyopathy when she was 24 years old and treated with carvedilol, digoxin, and enalapril. Her family history included dilated cardiomyopathy in her brother, sister, and son. She had been seemingly healthy until the morning of the day of admission. She suddenly recognized palpitation, dyspnea, and cold sweat when she was riding her bicycle. Though those symptoms were relieved with 15 minutes' rest, she felt disturbed pulse. She presented to our emergency department immediately.

She felt no symptom on admission. Chest radiogram showed cardiomegaly. Her electrocardiogram (ECG) showed sinus rhythm of 84 beats/min with occasional premature ventricular complexes (PVCs) (Fig. 1A). After admission, we evaluated her clinical picture. Her echocardiogram showed a markedly dilated left ventricle (Dd/Ds 77/63 mm) with the left ventricular ejection fraction of 17%. Blood tests revealed no significant abnormalities including electrolyte disturbance. Suddenly, recurrent ventricular tachycardia (VT) was observed on her monitoring ECG during the hospitalization (Fig. 1B). There were no significant triggers of

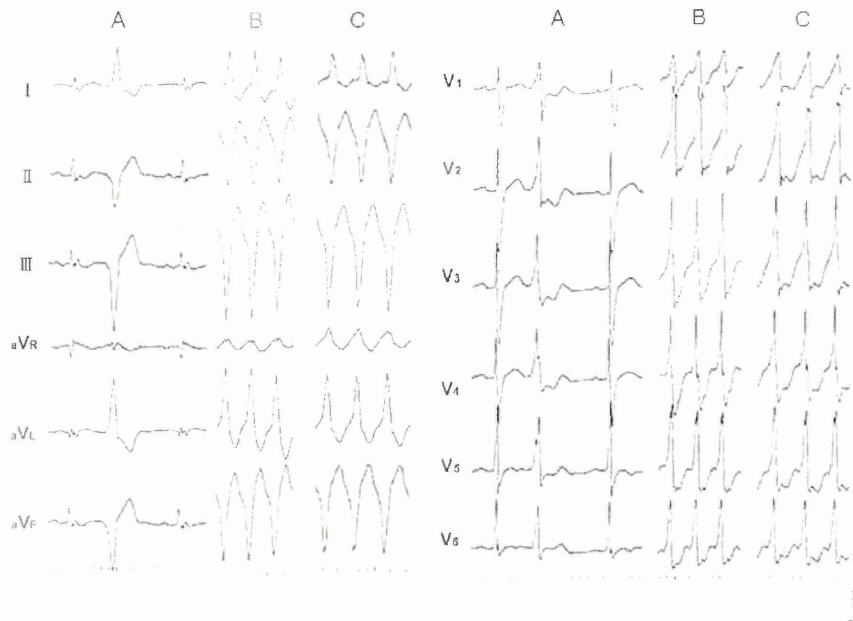


Figure 1. Twelve-lead electrocardiograms (ECGs) on admission and during ventricular tachycardia (VT) before and after amiodarone. The ECG showed sinus rhythm of 84 beats per minute with first degree atrio-ventricular block, and occasional premature ventricular complexes (PVC) (A). Before amiodarone administration, the QRS morphology of incessant VT was right bundle branch block morphology with superior axis (B). After amiodarone administration, the QRS morphology of VT was also similar to that of VT before amiodarone, but VT rate decreased to 150 beats per minute (C).

arrhythmia such as a change in drug dosage, electrolyte disturbance, infection, or exercise. VT rate was 170 beats/min and she complained of palpitation.

After 125 mg of amiodarone was administered intravenously over 10 minutes, continuous intravenous administration (40 mg per hour) was given. An hour after starting amiodarone, the VT rate decreased to 150 beats/min but the duration of VT was still prolonged (Fig. 1C). Moreover, the morphology of the initiating PVC was changed. Before amiodarone, VT was triggered by PVC of which the morphology differed from that of VT (Fig. 2A). After one hour of intravenous amiodarone, the culprit PVC in the baseline was completely eliminated, and then sustained VT was triggered by the PVC, whose morphology was virtually identical to the sustained VT (Fig. 2B).

During sinus rhythm, QRS duration was prolonged from 130 ms to 160 ms, and the corrected QT interval was also prolonged from 370 ms to 400 ms (Fig. 3). VT of more than 3 beats was found three times and they lasted in total for 4 minutes and 10 seconds in the 15-minute period before amiodarone. Before discontinuation of amiodarone, VT was found to occur 5 times and lasted for 9 minutes and 40 seconds in the 15-minute period.

We discontinued amiodarone, and administered 12 mg of nifekalant, pure IKr blocker, over 5 minutes intravenously followed by a continuous dose of 9 mg per hour. About 7 minutes after starting nifekalant, VT disappeared completely. QRS duration was not changed (160 ms), but the corrected

QT interval was markedly prolonged to 520 ms.

Administration of sotalol (80 mg per day) made it possible to withdraw nifekalant. Because her heart rate tended to be low, and an increase in β -blocker dosage was considered necessary, CRT-D implantation was conducted. After the increase of carvedilol to 10 mg per day, she was discharged from our hospital.

Discussion

Several studies have demonstrated the usefulness of intravenous amiodarone and it is now recommended as a first-line drug for treatment of VT (5). While intravenous amiodarone is generally regarded as a safe treatment, there are several reports on proarrhythmia inducing TdP under certain conditions including electrolyte imbalance (3, 4, 6, 7). In the present case, incessant monomorphic VT, not TdP, was induced after injection of intravenous amiodarone. As far as we know, this is the first report on monomorphic VT induced after amiodarone infusion. Moreover, the amiodarone efficacy in the treatment of stable VT has not been fully elucidated (8-10).

The incessant VT in this patient, who had structural heart disease, maintained regular beats and was reproducibly induced by relatively short coupled PVC. VT always terminated and reappeared spontaneously and the VT cycle length was gradually prolonged (about 10%) before spontaneous termination. These findings supported the reentrant mecha-

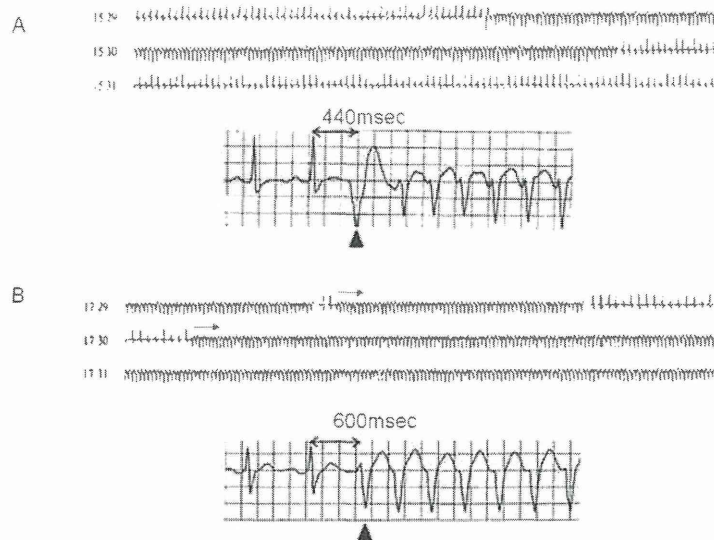


Figure 2. Recurrent ventricular tachycardia (VT) observed on the monitoring electrocardiogram (ECG) before and after amiodarone. Recurrent VT was suddenly observed on her monitoring ECG (A). After intravenous amiodarone, VT became more incessant and the duration of VT prolonged still more (B). Before amiodarone administration, relatively short coupled premature ventricular complex (PVC) (the coupling interval was 440 ms), of which morphology was different from that of VT, induced recurrent VT (A). After amiodarone, VT was reproducibly triggered by PVC of which morphology was same as that of VT and the coupling interval of initiating PVC was relatively longer (600 ms) (B).

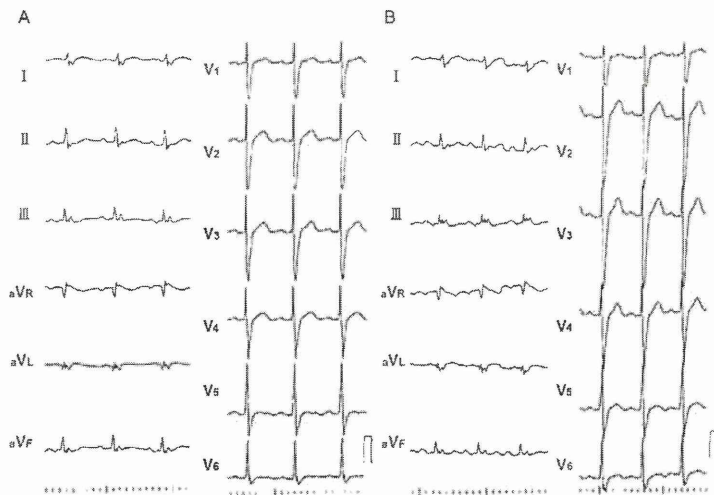


Figure 3. Twelve-lead electrocardiograms (ECGs) during sinus rhythm before and after amiodarone. Before amiodarone, QRS duration was 130 msec and QTc interval was 370 msec on the ECG (A). After amiodarone, QRS duration and QTc interval were prolonged to 160 msec and 400 msec (B).

nism of this VT.

Intravenous amiodarone inhibits sodium channels, inward L-type calcium channels, and has noncompetitive β -blockade effect, but the potassium channel blockade effect became more apparent after long-term therapy. It was possible that blockade of L-type calcium channels and β -blockade could suppress automaticity and triggered activity. However, in this case, the mechanism of VT was thought to

be likely due to re-entry, these effects can just slow the VT rate. The slight prolongation of QT interval can be explained by potassium channel blockade effect of intravenous amiodarone. The prolongation of QRS duration, the decline of VT rate, and the change of QRS morphology of the initiating PVC after intravenous amiodarone suggested that the acute effect of amiodarone infusion mainly developed sodium channel blockade. The coupling interval between the

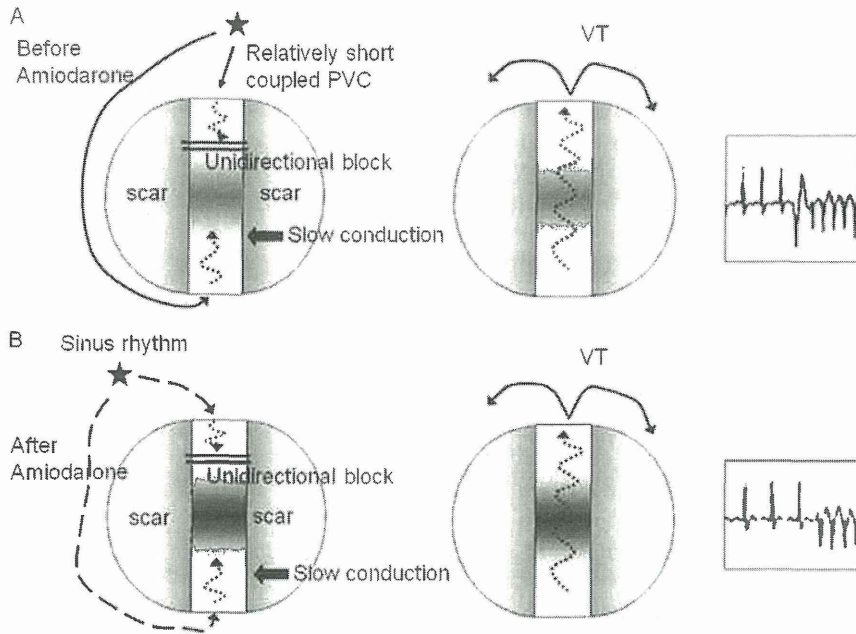


Figure 4. Illustration of postulated mechanism of ventricular tachycardia (VT) before and after amiodarone. Before amiodarone administration, relatively short coupled premature ventricular complex caused unidirectional block in critical slow pathway zone, and retrograde conduction formed the reentrant circuit resulting in recurrent VT (A). After amiodarone administration, its blocking effect of sodium channel could create the unidirectional block in the critical slow conduction zone even during sinus rhythm and induced the incessant monomorphic VT (B).

initiating PVC and the next beat of VT was nearly identical to VT cycle length.

We depicted the postulated mechanism of VT in this case as shown in Fig. 4. Sodium channel blockade of amiodarone was thought to create the unidirectional block in the critical slow conduction zone even during sinus rhythm and induced the incessant monomorphic VT as a proarrhythmia. At the time of admission, the morphology of occasional PVC was similar to that of documented incessant VT, and QRS duration was 150 ms, this was relatively longer than the QRS duration before amiodarone. These findings suggested that a similar proarrhythmic situation had occurred in this patient at that time for some reasons but the difference between the coupling intervals of PVCs at the time of admission and after amiodarone determined whether the arrhythmias were sustained or not. Subsequent intravenous nifekalant, which promptly inhibits IKr channels and prolongs effective refractory period of ventricular myocardium in the critical slow pathway, could make VT disappeared completely. This successful suppression of VT could result from combination effects of amiodarone and nifekalant.

It was possible that amiodarone suppressed the original initiating PVC and accordingly the initiating PVC was changed. The effects of amiodarone other than sodium channel blockade could affect initiating PVC. But, nifekalant, IKr inhibitor, which has little effect on sodium and calcium channels, swept the initiating PVC away. This indicated that the initiating PVC was due to re-entrant mechanism rather than abnormal automaticity and triggered activity which de-

pended on mainly intracellular sodium and calcium ion concentrations. In addition, (i) amiodarone usually suppressed the abnormal automaticity and triggered activity, (ii) a similar QRS prolongation was observed at the time of hospitalization and after amiodarone when similar PVC were found and VT worsened, (iii) the coupling interval between the initiating PVC and the preceding QRS was nearly constant, (iv) sustained VT was suppressed concomitant with the complete suppression of the PVCs after nifekalant administration. These also support our re-entrant hypothesis that sodium channel blockade affected on this patient. Furthermore, Duff et al demonstrated experimentally that sodium channel blocker precipitated monomorphic VT and its inducibility was suppressed by potassium channel blocker (11). Their experiment also supports our hypothesis. However, we could not completely exclude the possibility of initiating PVC from the exit-site of critical slow conduction after amiodarone. Initiating PVC from the exit-site could be analogous to the QRS morphology of VT and the coupling interval between the 1st and 2nd beat of VT could be similar to VT cycle length.

We encountered incessant monomorphic VT induced after injection of intravenous amiodarone. It is important to be aware of the proarrhythmic effect of amiodarone which may lead to an electrical storm of monomorphic VT.

The authors state that they have no Conflict of Interest (COI).