Abrupt Heart Rate Fallings in a Patient with Biventricular Pacing: Latent Risk for Exacerbation of Heart Failure

HIRO KAWATA, M.D.,* TAKASHI NODA, M.D.,* YUKO YAMADA, M.D.,* HIDEO OKAMURA, M.D.,* HIROYUKI NAKAJIMA, M.D.,† JUNJIRO KOBAYASHI, M.D.,† and SHIRO KAMAKURA, M.D.*

From the *Division of Cardiology, Department of Internal Medicine, National Cardiovascular Center, Suita, Japan; and †Department of Cardiovascular Surgery, National Cardiovascular Center, Suita, Japan

This case report describes abrupt heart rate fallings below the lower pacing rate limit in a patient with cardiac resynchronization therapy (CRT). Interrogated information including stored episodes or data regarding the lead did not show any device problems and only simultaneous intracardiac electrogram revealed the cause, T-wave oversensing during biventricular pacing. At this moment, CRT has become an established modality for patients with severe heart failure. However, bradycardia below the lower rate limit during biventricular pacing due to T-wave oversensing would exacerbate heart failure in patients with CRT. We should notice this latent risk and correct the malfunction immediately. (PACE 2012; 35:e55–e58)

T-wave oversensing, CRT, device malfunction

Introduction

Many studies have demonstrated that cardiac resynchronization therapy (CRT) is established modality for patients with severe heart failure.[1,2] Not only heart failure symptoms, but also the rate of mortality or hospitalization were improved by CRT. To respond to CRT, there are several factors. It is important to capture the ventricles consistently by biventricular pacing with appropriate heart rate and we should be well aware of CRT device malfunction.[3] Postpacing T-wave oversensing is one of pacing device malfunction and can cause inappropriate bradycardia.[4] This phenomenon appears only after pacing, so it cannot be stored as episodes on the device leading to be overlooked. Here, we report abrupt heart rate fallings below the lower pacing rate limit in a patient with CRT. Only simultaneous intracardiac electrogram (EGM) revealed the cause, which was T-wave oversensing during biventricular pacing.

Case Report

The patient was a 68-year-old man who underwent a valve replacement for aortic regurgitation complicated with left ventricular dysfunction. He developed atrioventricular block and received a pacemaker in 1994. Subsequently, he developed dyspnea on effort with New York Heart Association functional class III. On echocardiography, the left ventricule was markedly dilated and its function was severely impaired with a left ventricular ejection fraction of 24%. Both interventricular and intraventricular dyssynchrony were confirmed. He underwent removal of previous pacemaker and implantation of CRT device with defibrillator (CRT-D) (Concerto C174AWK, Medtronic Inc., Minneapolis, MN, USA). All procedures were performed successfully without any complication. Initially, the lower pacing rate limit was set at 70 beats per minute (bpm). He continued his hospitalization to adjust the medical therapy for heart failure and CRT-D. Twelve days after the implantation, his monitor electrocardiogram displayed abrupt heart rate fallings below the lower pacing rate limit (Fig. 1). Interrogated and checked information including the lead impedance or capture threshold did not reveal any device problem. There were no events that suggested noises due to the lead fracture or electromagnetic interference. Close monitoring was continued. Finally, we could get intracardiac EGM during abnormal bradycardia pacing simultaneously (Fig. 2). The intracardiac EGM showed T-wave oversensing during biventricular pacing. Time from BV (biventricular pacing spike) to TS (ventricular sense) was 394 ms and TS maker located near the T wave. On the other hand, time from TS to BV was 850 ms, which was equal to the lower pacing rate limit at 70 bpm. These facts are consistent with the fact

Address for reprints: Takashi Noda, M.D., Division of Cardiology, Department of Internal Medicine, National Cardiovascular Center, 5-7-1 Fujishiro-dai, Suita, Osaka, 565-8565 Japan. Fax: 81-6-6872-7486; e-mail: tnoda@hsp.ncvc.go.jp

Received February 10, 2010; revised March 16, 2010; accepted May 21, 2010.

doi: 10.1111/j.1540-8159.2010.02855.x

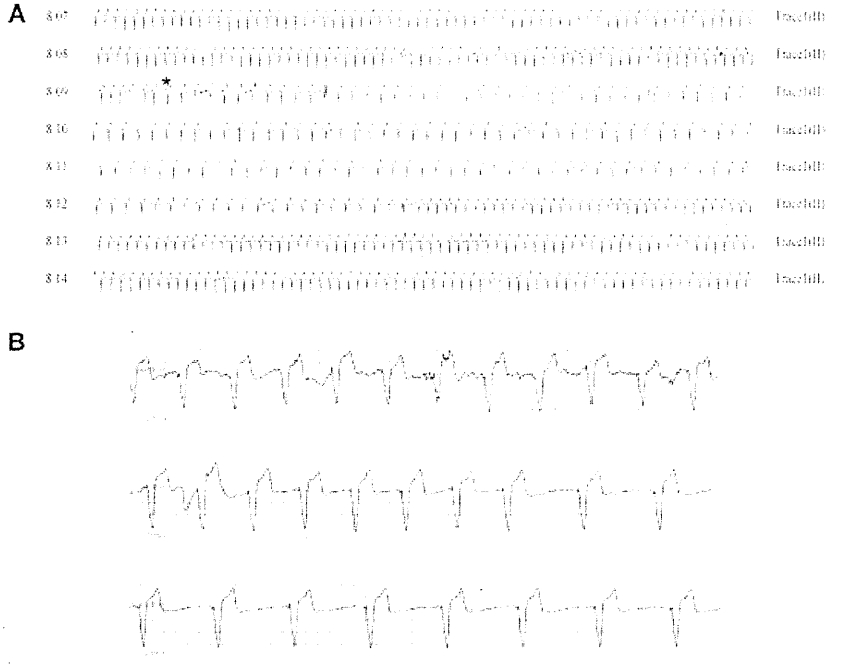

Figure 1. *Abrupt heart rate fallings below the lower pacing rate limit during biventricular pacing. (A) The monitor electrocardiogram showed that abrupt bradycardia at 47 bpm started at the middle of the third line (asterisk) and his heart rate spontaneously recovered to 70 bpm after a while. (B) The enlarged figure of the monitor electrocardiogram showed abrupt bradycardia at 47 bpm.*

of abrupt pacing heart rate fallings at 47 bpm. We changed ventricular blanking period after the pacing from 200 ms to 430 ms, and T-wave oversensing during biventricular pacing disappeared. After adjustment of medical therapy for heart failure, he was discharged. One month later, he complained of multiple presyncopal episodes and T-wave oversensing on intracardiac EGM were observed again. T-wave sensing occurred after the postpacing blanking period. Finally, we adjusted programmed sensitivity from 0.6 mV to 0.9 mV and T-wave oversensing during biventricular pacing has never been observed since then.

Discussion

T-wave oversensing remains an annoying problem in currently available implantable cardioverter defibrillators (ICDs) and CRT-D.[5–7] T-wave oversensing is one of the most common ventricular oversensing malfunction, occurring in 14% of the patients.[8] T-wave oversensing can be divided into three categories: Postpacing, small R wave, and large R wave. The most famous malfunction regarding T-wave oversensing is with small R wave. The ICDs automatically adjust sensitivity in relation to the amplitude of the preceding R wave. At the end of the blanking period after each sensed ventricular event, sensitivity is decreased to a starting value related to the amplitude of the sensed R wave and then decreases with time to a minimum value. This auto-adjusting sensitivity after a sensed ventricular event is useful for detecting ventricular fibrillation (VF) and avoiding T-wave oversensing during sinus rhythm. However, it is sometimes difficult to avoid T-wave oversensing in ICD or CRT-D patients with high T-wave/R-wave ratio. Patients with an ICD or CRT-D whose device shows low-amplitude R waves may require lower minimum sensing thresholds to secure the detection of VF. There is a report regarding Brugada syndrome that the amplitude of T wave decreased and T-wave/R-wave ratio changed spontaneously in the clinical course, which led T-wave oversensing and inappropriate shock.[9] This type of T-wave oversensing is also reported in other heart diseases such as hypertrophic cardiomyopathy and dilated cardiomyopathy.[10] In this situation, we try to manage T-wave oversensing noninvasively by decreasing the ventricular sensitivity, programming longer postventricular sensing refractory periods, and increasing the detection interval count in the tachycardia zone. However, lead revision or the device change to another brand with

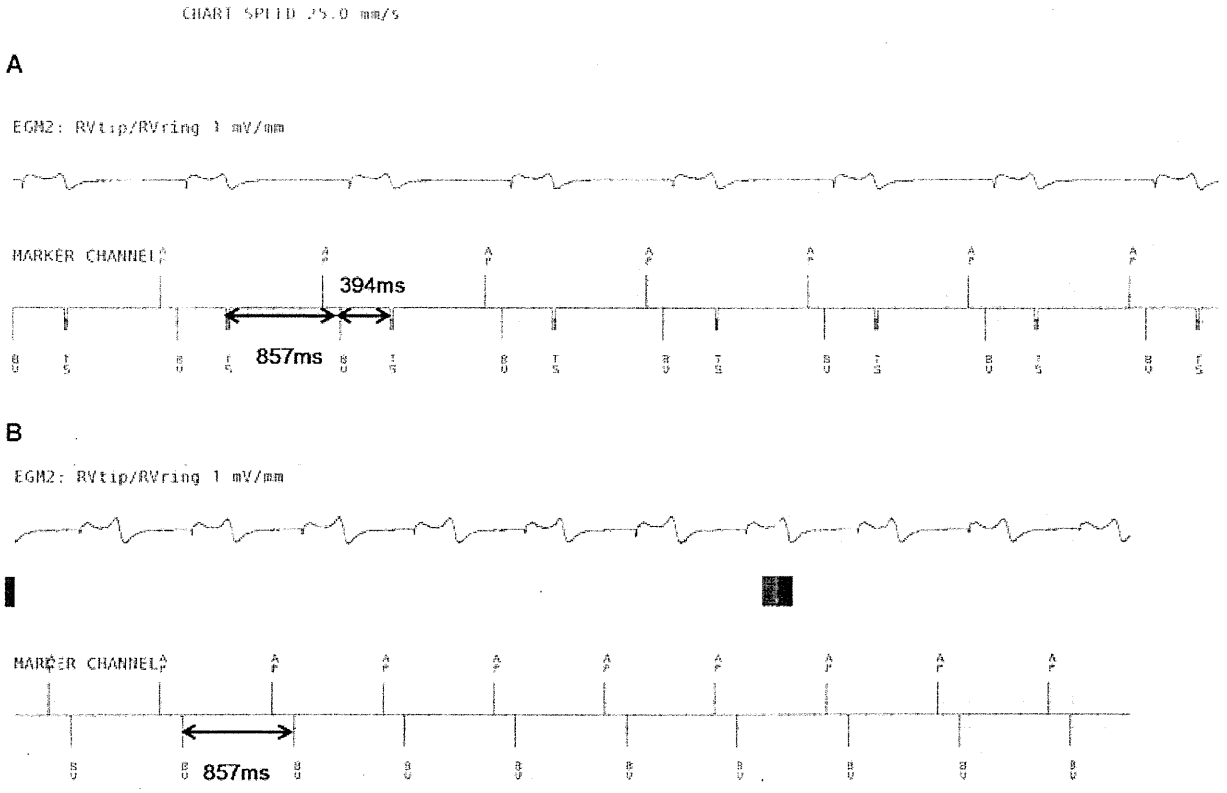

Figure 2. *Intracardiac electrogram during abnormal bradycardia pacing. (A) T-wave oversensing occurred at ventricular sensitivity of 0.6 mV. Time from BV (biventricular pacing spike) to TS (ventricular sense) was 394 ms and TS maker located near the T wave. And time from TS to BV was 850 ms, which was equal to the lower pacing rate limit at 70 bpm. (B) T-wave oversensing disappeared after setting ventricular sensitivity by 0.9 mV.*

more specific filtering to reject T-wave is often necessary.

Postpacing T-wave oversensing can cause inappropriate bradycardia pacing or delivery of antitachycardia pacing at wrong rate.[11] This phenomenon appears only after pacing, so it does not induce inappropriate VF detection. However, it could cause abnormal bradycardia below the lower pacing rate limit, which could be a latent risk for exacerbation of heart failure in CRT patients. Postpacing T-wave oversensing is relatively rare, partly because this problem is not recognized as tachycardia event and is not stored at device EGM. After a pacing pulse, the starting point of the sensitivity threshold is different from that initiated by sensing a spontaneous R wave. A longer ventricular blanking period is required after a ventricular paced event to avoid sensing of T wave of paced beats. In most ICD or CRT-D, ventricular blanking period after bradycardia pace is programmable. In our case, we extended postpacing blanking period in order to avoid postpacing T-wave oversensing. However, maximal extension of postpacing blanking period could not eliminate this problem so that we had to reduce programmed sensitivity. In our case, T-wave oversensing was transient. Although we could not elucidate the cause of this phenomenon, electrolytes balance, body position, and QT interval were considered as the factors of transient manner of this problem. Fortunately, we could detect this event during the hospitalization. However, these events were not recorded on their device and frequently overlooked. Although our patient did not develop syncope, this oversensing might lead to catastrophic syncopal event. Moreover, inappropriate bradycardia pacing could cause heart failure deterioration, especially in a CRT-D patient. We should recognize that T-wave oversensing during biventricular pacing might be overlooked and the only interrogated information is inadequate to evaluate malfunction of CRT device.

Conclusion

Here we experienced abrupt heart rate fallings below the lower pacing rate limit because of postpacing T-wave oversensing in a patient with

CRT-D. Postpacing T-wave oversensing is rare and this problem might be overlooked. As the number of patients with CRT-D will increase more and more in the future, clinicians treating CRT-D patients should be well aware of this malfunction.

References

1. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, Tavazzi L; Cardiac Resynchronization-Heart Failure (CARE-HF) Study Investigators. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med 2005; 352:1539–1549.
2. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, Carson P, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med 2004; 350:2140–2150.
3. Mullens W, Grimm RA, Verga T, Dresing T, Starling RC, Wilkoff BL, Tang WH. Insights from a cardiac resynchronization optimization clinic as part of a heart failure disease management program. J Am Coll Cardiol 2009; 53:765–773.
4. Swerdlow CD, Friedman PA. Advanced ICD troubleshooting: Part I. Pacing Clin Electrophysiol 2005; 28:1322–1346.
5. Erven L, Schalij MJ. Troubleshooting implantable cardioverter-defibrillator related problems. Heart 2008; 94:649–660.
6. Koul AK, Keller S, Clancy JF, Lampert R, Batsford WP, Rosenfeld LE. Hypercalemia induced T wave oversensing leading to loss of biventricular pacing and inappropriate ICD shocks. Pacing Clin Electrophysiol 2004; 27:681–683.
7. Gilliam FR. T-wave oversensing in implantable cardiac defibrillators is due to technical failure of device sensing. J Cardiovasc Electrophysiol 2006; 17:553–556.
8. Weretka S, Michaelsen J, Becker R, Karle CA, Voss F, Hilbel T, Osswald BR, et al. Ventricular oversensing: A study of 101 patients implanted with dual chamber defibrillators and two different lead systems. Pacing Clin Electrophysiol 2003; 26(pt 1):65–70.
9. Porres JM, Brugada J, Marco P, Garcia F, Azcarate B. T wave oversensing by a cardioverter defibrillator implanted in a patient with the Brugada syndrome. Pacing Clin Electrophysiol 2004; 27:1563–1565.
10. Washizuka T, Chinushi M, Tagawa M, Kasai H, Watanabe H, Hosaka Y, Yamashita F, et al. Inappropriate discharges by fourth generation implantable cardioverter defibrillators in patients with ventricular arrhythmias. Jpn Circ J 2001; 65:927–930.
11. Manolis AG, Chatzis DG, Kouvelas K, Kyriakides ZS. Partial inhibition of ongoing antitachycardia pacing sequence due to T-wave oversensing. Pacing Clin Electrophysiol 2008; 31:780–781.

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

Hiroshi Watanabe, MD, PhD, FESC; Akihiko Nogami, MD, PhD; Kimie Ohkubo, MD, PhD; Hiro Kawata, MD, PhD; Yuka Hayashi, MD; Taisuke Ishikawa, DVM; Takeru Makiyama, MD, PhD; Satomi Nagao, MD; Nobue Yagihara, MD; Naofumi Takehara, MD, PhD; Yuichiro Kawamura, MD, PhD; Akinori Sato, MD, PhD; Kazuki Okamura, MD, PhD; Yukio Hosaka, MD, PhD; Masahito Sato, MD, PhD; Satoki Fukae, MD, PhD; Masaomi Chinushi, MD, PhD; Hirotaka Oda, MD, PhD; Masaaki Okabe, MD, PhD; Akinori Kimura, MD, PhD; Koji Maemura, MD, PhD; Ichiro Watanabe, MD, PhD, FHRS; Shiro Kamakura, MD, PhD; Minoru Horie, MD, PhD; Yoshifusa Aizawa, MD, PhD; Wataru Shimizu, MD, PhD; Naomasa Makita, MD, PhD

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 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]

Clinical Perspective on p 881

Received February 2, 2011; accepted October 5, 2011.

From the Division of Cardiology (H.W., Y.H., S.N., N.Y., A.S., K.O., M.C., Y.A.), Niigata University School of Medicine, Niigata; Division of Heart Rhythm Management (A.N.), Yokohama Rosai Hospital, Yokohama; Division of Cardiology (K.O., I.W.), Department of Medicine, Nihon University School of Medicine, Tokyo; Division of Arrhythmia and Electrophysiology (H.K., S.K., W.S.), Department of Cardiovascular Medicine, National Cerebral and Cardiovascular Center, Suita; Department of Molecular Pathogenesis (T.I., A.K.), Medical Research Institute, Tokyo Medical and Dental University, Tokyo; Department of Cardiovascular Medicine (T.M.), Kyoto University Graduate School of Medicine, Kyoto; Department of Internal Medicine (N.T., Y.K.), Division of Cardiovascular Respiratory and Neurology, Asahikawa Medical University, Asahikawa; Department of Cardiology (Y.H., H.O.), Niigata City General Hospital, Niigata; Cardiovascular Center (M.S., M.O.), Tachikawa General Hospital, Nagaoka; Departments of Cardiovascular Medicine (S.F., K.M.) and Molecular Physiology (N.M.), Nagasaki University Graduate School of Biomedical Sciences, Nagasaki; Department of Cardiovascular and Respiratory Medicine (M.H.), Shiga University of Medical Science, Shiga, Japan.

Correspondence to Hiroshi Watanabe, MD, PhD, FESC, Division of Cardiology, Niigata University Graduate School of Medical and Dental Sciences, 1-754 Asahimachidori, Niigata 951-8510 Japan. E-mail hiroshi7@med.niigata-u.ac.jp

Circ Arrhythm Electrophysiol **is available at http://circep.ahajournals.org** **DOI: 10.1161/CIRCEP.111.963983**

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 $\geq$0.1 mV $\geq$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-hβ1) encoding CD8 and the human sodium channel β1 subunit (hβ1) to visually identify cells expressing heterologous hβ1 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/LΩ. 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 $CaCl_2$, 1 $MgCl_2$, 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

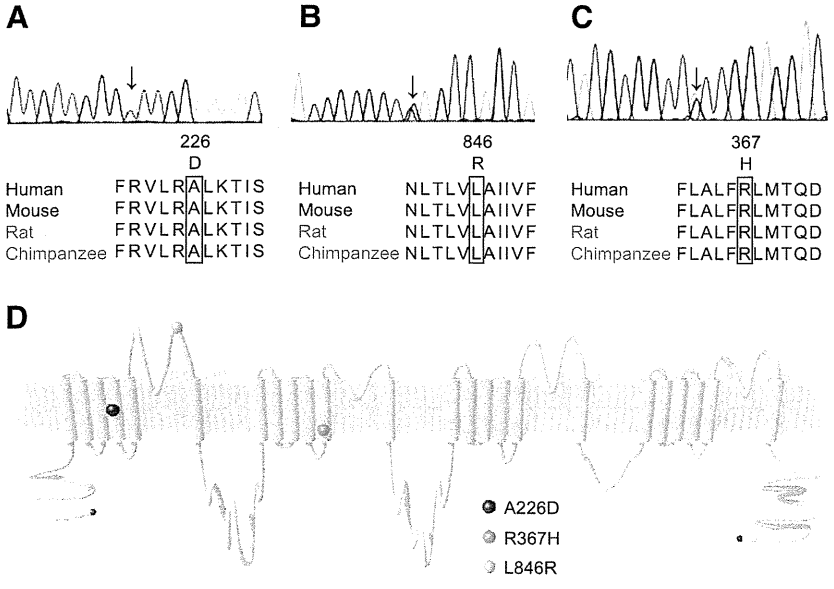

Figure 1. Mutations in *SCN5A* identified in patients with idiopathic ventricular fibrillation associated with early repolarization. **A**, The c.677C→A mutation in *SCN5A* resulting in p.A226D found in patient 1. **B**, The c.2537T→G mutation in *SCN5A*, resulting in p.L846R found in patient 2. **C**, 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 al[27]). **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 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.[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

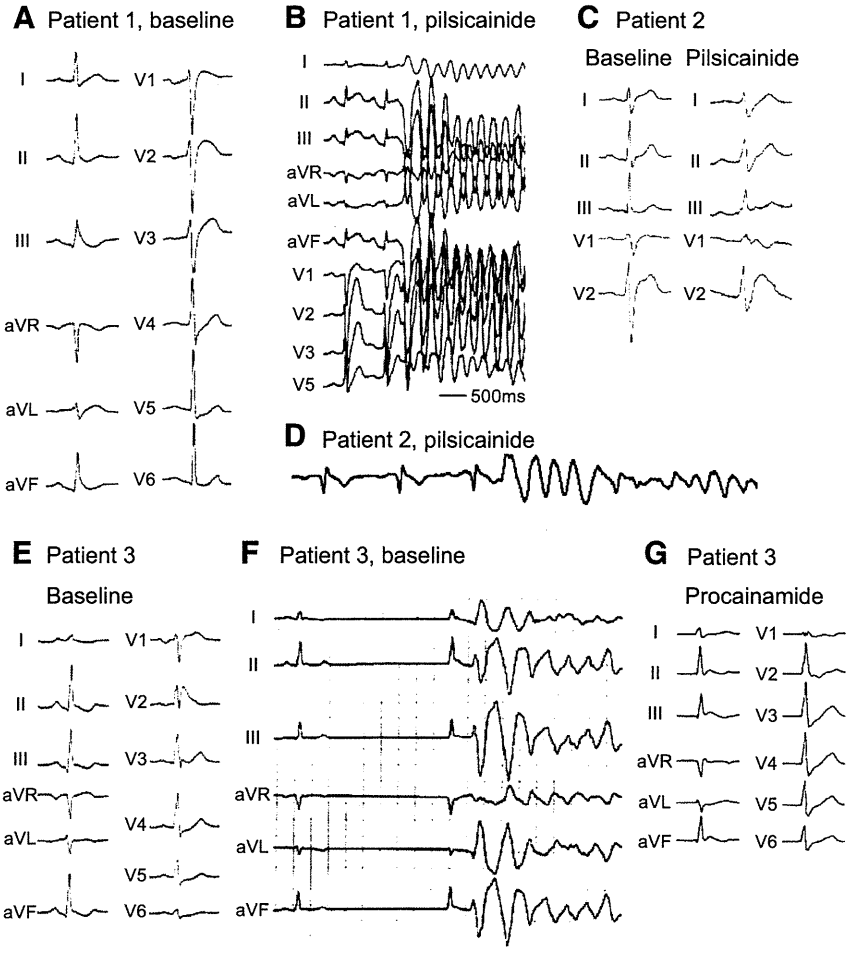

Figure 2. Electrocardiograms of patients with idiopathic ventricular fibrillation and a mutation in *SCN5A*. **A**, Early repolarization was present in the inferior and right precordial leads in patient 1. **B**, After administration of pilsicainide, early repolarization was augmented and ventricular 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]

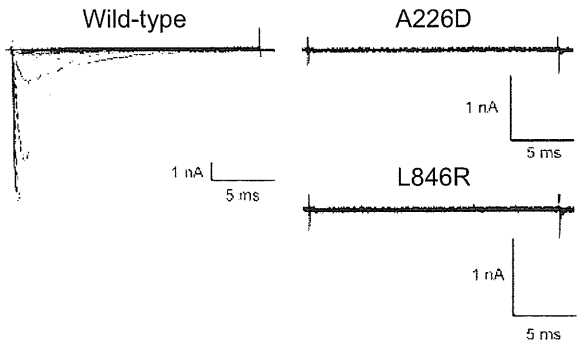

Figure 3. Electrophysiological characteristics of the *SCN5A* mutants. Representative traces of sodium current demonstrating that all of the mutant channels failed to generate any currents. We previously reported that R367H mutant fails to generate any currents.[27]

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

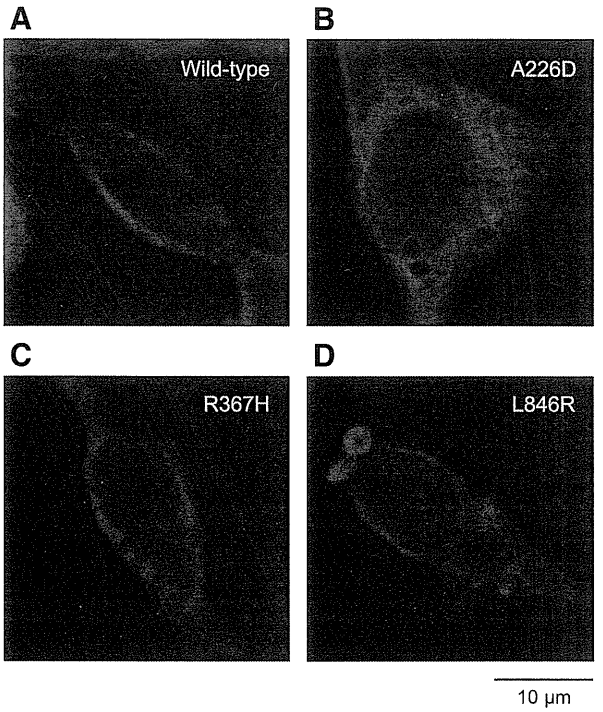

Figure 4. Representative confocal microscopy images. **A**, Cells expressing wild-type SCN5A channels showed marked peripheral fluorescence. **B**, Cells expressing A226D channels showed cytoplasmic fluorescence. **C** and **D**, Cells expressing R367H channels and those expressing L846R channels showed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

We thank Shigenori Terada at Akita University and Yoko Yanagida at Miyazaki Hospital for their assistance in performing this work.

Sources of Funding

This work was supported by grants from Ministry of Health, Labor, and Welfare of Japan (2010-145); Ministry of Education, Culture, Sports, Science and Technology, Japan (2010-22790696), and Grant-in-Aid for Scientific Research on Innovative Areas (HD Physiology) 22136007 (NM); Takeda Science Foundation 2010; and Japan Heart Foundation/Novartis Grant for Research Award on Molecular and Cellular Cardiology 2010.

References

1. Klatsky AL, Oehm R, Cooper RA, Udaltsova N, Armstrong MA. The early repolarization normal variant electrocardiogram: correlates and consequences. *Am J Med.* 2003;115:171–177.
2. Osborn JJ. Experimental hypothermia; respiratory and blood pH changes in relation to cardiac function. *Am J Physiol.* 1953;175:389–398.
3. Maruyama M, Atarashi H, Ino T, Kishida H. Osborn waves associated with ventricular fibrillation in a patient with vasospastic angina. *J Cardiovasc Electrophysiol.* 2002;13:486–489.
4. Shinde R, Shinde S, Makhale C, Grant P, Sathe S, Durairaj M, Lokhandwala Y, Di Diego J, Antzelevitch C. Occurrence of "J waves" in 12-lead ECG as a marker of acute ischemia and their cellular basis. *Pacing Clin Electrophysiol.* 2007;30:817–819.
5. Haissaguerre M, Derval N, Sacher F, Jesel L, Deisenhofer I, de Roy L, Pasquie JL, Nogami A, Babuty D, Yli-Mayry S, De Chillou C, Scanu P, Mabo P, Matsuo S, Probst V, Le Scouarnec S, Defaye P, Schlaepfer J, Rostock T, Lacroix D, Lamaison D, Lavergne T, Aizawa Y, Englund A, Anselme F, O'Neill M, Hocini M, Lim KT, Knecht S, Veenhuyzen GD, Bordachar P, Chauvin M, Jais P, Coureau G, Chene G, Klein GJ, Clementy J. Sudden cardiac arrest associated with early repolarization. *N Engl J Med.* 2008;358:2016–2023.
6. Rosso R, Kogan E, Belhassen B, Rozovski U, Scheinman MM, Zeltser D, Halkin A, Steinvil A, Heller K, Glikson M, Katz A, Viskin S. J-point elevation in survivors of primary ventricular fibrillation and matched control subjects: incidence and clinical significance. *J Am Coll Cardiol.* 2008;52:1231–1238.
7. Tikkanen JT, Anttonen O, Junttila MJ, Aro AL, Kerola T, Rissanen HA, Reunanen A, Huikuri HV. Long-term outcome associated with early repolarization on electrocardiography. *N Engl J Med.* 2009;361:2529–2537.

8. Nam GB, Ko KH, Kim J, Park KM, Rhee KS, Choi KJ, Kim YH, Antzelevitch C. Mode of onset of ventricular fibrillation in patients with early repolarization pattern vs. Brugada syndrome. *Eur Heart J.* 2009; 31:330–339.
9. Reinhard W, Kaess BM, Debiec R, Nelson CP, Stark K, Tobin MD, Macfarlane PW, Tomaszewski M, Samani NJ, Hengstenberg C. Heritability of early repolarization: a population-based study. *Circ Cardiovasc Genet.* 2011;4:134–138.
10. Lehnart SE, Ackerman MJ, Benson DW Jr, Brugada R, Clancy CE, Donahue JK, George AL Jr, Grant AO, Groft SC, January CT, Lathrop DA, Lederer WJ, Makielski JC, Mohler PJ, Moss A, Nerbonne JM, Olson TM, Przywara DA, Towbin JA, Wang LH, Marks AR. Inherited arrhythmias: a National Heart, Lung, and Blood Institute and Office of Rare Diseases workshop consensus report about the diagnosis, phenotyping, molecular mechanisms, and therapeutic approaches for primary cardiomyopathies of gene mutations affecting ion channel function. *Circulation.* 2007;116:2325–2345.
11. Haissaguerre M, Chatel S, Sacher F, Weerasooriya R, Probst V, Loussouarn G, Horlitz M, Liersch R, Schulze-Bahr E, Wilde A, Kaab S, Koster J, Rudy Y, Le Marec H, Schott JJ. Ventricular fibrillation with prominent early repolarization associated with a rare variant of KCNJ8/KATP channel. *J Cardiovasc Electrophysiol.* 2009;20:93–98.
12. Burashnikov E, Pfeiffer R, Barajas-Martinez H, Delpon E, Hu D, Desai M, Borggrefe M, Haissaguerre M, Kanter R, Pollevick GD, Guerchicoff A, Laino R, Marieb M, Nademanee K, Nam GB, Robles R, Schimpf R, Stapleton DH, Viskin S, Winters S, Wolpert C, Zimmern S, Veltmann C, Antzelevitch C. Mutations in the cardiac L-type calcium channel associated with inherited J-wave syndromes and sudden cardiac death. *Heart Rhythm.* 2010;7:1872–1882.
13. Valdivia CR, Medeiros-Domingo A, Ye B, Shen WK, Algiers TJ, Ackerman MJ, Makielski JC. Loss-of-function mutation of the SCN3B-encoded sodium channel beta3 subunit associated with a case of idiopathic ventricular fibrillation. *Cardiovasc Res.* 2010;86:392–400.
14. Medeiros-Domingo A, Tan BH, Crotti L, Tester DJ, Eckhardt L, Cuoretti A, Kroboth SL, Song C, Zhou Q, Kopp D, Schwartz PJ, Makielski JC, Ackerman MJ. Gain-of-function mutation, S422L, in the KCNJ8-encoded cardiac K ATP channel Kir6.1 as a pathogenic substrate for J wave syndromes. *Heart Rhythm.* 2010;7:1466–1471.
15. Moss AJ, Schwartz PJ, Crampton RS, Locati E, Carleen E. The long QT syndrome: a prospective international study. *Circulation.* 1985;71:17–21.
16. Gaita F, Giustetto C, Bianchi F, Wolpert C, Schimpf R, Riccardi R, Grossi S, Richiardi E, Borggrefe M. Short QT Syndrome: a familial cause of sudden death. *Circulation.* 2003;108:965–970.
17. Wilde AA, Antzelevitch C, Borggrefe M, Brugada J, Brugada R, Brugada P, Corrado D, Hauer RN, Kass RS, Nademanee K, Priori SG, Towbin JA. Proposed diagnostic criteria for the Brugada syndrome: consensus report. *Circulation.* 2002;106:2514–2519.
18. Watanabe H, Makiyama T, Koyama T, Kannankeril PJ, Seto S, Okamura K, Oda H, Itoh H, Okada M, Tanabe N, Yagihara N, Kamakura S, Horie M, Aizawa Y, Shimizu W. High prevalence of early repolarization in short QT syndrome. *Heart Rhythm.* 2010;7:647–652.
19. Splawski I, Shen J, Timothy KW, Lehmann MH, Priori S, Robinson JL, Moss AJ, Schwartz PJ, Towbin JA, Vincent GM, Keating MT. Spectrum of mutations in long-QT syndrome genes. KVLQT1, HERG, SCN5A, KCNE1, and KCNE2. *Circulation.* 2000;102:1178–1185.
20. Wang Q, Li Z, Shen J, Keating MT. Genomic organization of the human SCN5A gene encoding the cardiac sodium channel. *Genomics.* 1996; 34:9–16.
21. Tester DJ, Will ML, Ackerman MJ. Mutation detection in congenital long QT syndrome: cardiac channel gene screen using PCR, dHPLC, and direct DNA sequencing. *Methods Mol Med.* 2006;128:181–207.
22. Makita N, Behr E, Shimizu W, Horie M, Sunami A, Crotti L, Schulze-Bahr E, Fukuhara S, Mochizuki N, Makiyama T, Itoh H, Christiansen M, McKeown P, Miyamoto K, Kamakura S, Tsutsui H, Schwartz PJ, George AL Jr, Roden DM. The E1784K mutation in SCN5A is associated with mixed clinical phenotype of type 3 long QT syndrome. *J Clin Invest.* 2008;118:2219–2229.
23. Liu K, Yang T, Viswanathan PC, Roden DM. New mechanism contributing to drug-induced arrhythmia: rescue of a misprocessed LQT3 mutant. *Circulation.* 2005;112:3239–3246.
24. Sato A, Arimura T, Makita N, Ishikawa T, Aizawa Y, Ushinohama H, Kimura A. Novel mechanisms of trafficking defect caused by KCNQ1 mutations found in long QT syndrome. *J Biol Chem.* 2009;284: 35122–35133.
25. Antzelevitch C, Brugada P, Borggrefe M, Brugada J, Brugada R, Corrado D, Gussak I, LeMarec H, Nademanee K, Perez Riera AR, Shimizu W, Schulze-Bahr E, Tan H, Wilde A. Brugada syndrome: report of the second consensus conference: endorsed by the Heart Rhythm Society and the European Heart Rhythm Association. *Circulation.* 2005;111: 659–670.
26. Josephson ME. Electrophysiologic investigation: general concepts. In: *Clinical Cardiac Electrophysiology: Techniques and Interpretations.* 4th ed. Lippincott Williams & Wilkins, 2008:20–68.
27. Takehara N, Makita N, Kawabe J, Sato N, Kawamura Y, Kitabatake A, Kikuchi K. A cardiac sodium channel mutation identified in Brugada syndrome associated with atrial standstill. *J Intern Med.* 2004;255: 137–142.
28. Chen Q, Kirsch GE, Zhang D, Brugada R, Brugada J, Brugada P, Potenza D, Moya A, Borggrefe M, Breithardt G, Ortiz-Lopez R, Wang Z, Antzelevitch C, O'Brien RE, Schulze-Bahr E, Keating MT, Towbin JA, Wang Q. Genetic basis and molecular mechanism for idiopathic ventricular fibrillation. *Nature.* 1998;392:293–296.
29. Schott JJ, Alshinawi C, Kyndt F, Probst V, Hoorntje TM, Hulsbeek M, Wilde AA, Escande D, Mannens MM, Le Marec H. Cardiac conduction defects associate with mutations in SCN5A. *Nat Genet.* 1999;23:20–21.
30. Benson DW, Wang DW, Dyment M, Knilans TK, Fish FA, Strieper MJ, Rhodes TH, George AL Jr. Congenital sick sinus syndrome caused by recessive mutations in the cardiac sodium channel gene (SCN5A). *J Clin Invest.* 2003;112:1019–1028.
31. Yan GX, Antzelevitch C. Cellular basis for the electrocardiographic J wave. *Circulation.* 1996;93:372–379.
32. Yan GX, Lankipalli RS, Burke JF, Musco S, Kowey PR. Ventricular repolarization components on the electrocardiogram: cellular basis and clinical significance. *J Am Coll Cardiol.* 2003;42:401–409.
33. Antzelevitch C, Yan GX. J wave syndromes. *Heart Rhythm.* 2010;7: 549–558.
34. Ruan Y, Liu N, Priori SG. Sodium channel mutations and arrhythmias. *Nat Rev Cardiol.* 2009;6:337–348.
35. Viskin S, Zeltser D, Ish-Shalom M, Katz A, Glikson M, Justo D, Tekes-Manova D, Belhassen B. Is idiopathic ventricular fibrillation a short QT syndrome? Comparison of QT intervals of patients with idiopathic ventricular fibrillation and healthy controls. *Heart Rhythm.* 2004;1:587–591.
36. Antzelevitch C, Pollevick GD, Cordeiro JM, Casis O, Sanguinetti MC, Aizawa Y, Guerchicoff A, Pfeiffer R, Oliva A, Wollnik B, Gelber P, Bonaros EP Jr, Burashnikov E, Wu Y, Sargent JD, Schickel S, Oberheiden R, Bhatia A, Hsu LF, Haissaguerre M, Schimpf R, Borggrefe M, Wolpert C. Loss-of-function mutations in the cardiac calcium channel underlie a new clinical entity characterized by ST-segment elevation, short QT intervals, and sudden cardiac death. *Circulation.* 2007;15: 442–449.
37. Hong K, Berruezo-Sanchez A, Poungvarin N, Oliva A, Vatta M, Brugada J, Brugada P, Towbin JA, Dumaine R, Pinero-Galvez C, Antzelevitch C, Brugada R. Phenotypic characterization of a large European family with Brugada syndrome displaying a sudden unexpected death syndrome mutation in SCN5A. *J Cardiovasc Electrophysiol.* 2004;15:64–69.
38. Miyazaki T, Mitamura H, Miyoshi S, Soejima K, Aizawa Y, Ogawa S. Autonomic and antiarrhythmic drug modulation of ST segment elevation in patients with Brugada syndrome. *J Am Coll Cardiol.* 1996;27: 1061–1070.
39. Watanabe A, Fukushima Kusano K, Morita H, Miura D, Sumida W, Hiramatsu S, Banba K, Nishii N, Nagase S, Nakamura K, Sakuragi S, Ohe T. Low-dose isoproterenol for repetitive ventricular arrhythmia in patients with Brugada syndrome. *Eur Heart J.* 2006;27:1579–1583.
40. Belhassen B, Glick A, Viskin S. Efficacy of quinidine in high-risk patients with Brugada syndrome. *Circulation.* 2004;110:1731–1737.
41. Haissaguerre M, Sacher F, Nogami A, Komiya N, Bernard A, Probst V, Yli-Mayry S, Defaye P, Aizawa Y, Frank R, Mantovan R, Cappato R, Wolpert C, Leenhardt A, de Roy L, Heidbuchel H, Deisenhofer I, Arentz T, Pasquie JL, Weerasooriya R, Hocini M, Jais P, Derval N, Bordachar P, Clementy J. Characteristics of recurrent ventricular fibrillation associated with inferolateral early repolarization role of drug therapy. *J Am Coll Cardiol.* 2009;53:612–619.
42. Viswanathan PC, Balser JR. Inherited sodium channelopathies: a continuum of channel dysfunction. *Trends Cardiovasc Med.* 2004;14: 28–35.
43. Aizawa Y, Tamura M, Chinushi M, Naitoh N, Uchiyama H, Kusano Y, Hosono H, Shibata A. Idiopathic ventricular fibrillation and bradycardia-dependent intraventricular block. *Am Heart J.* 1993;126: 1473–1474.

44. Mizumaki K, Fujiki A, Nishida K, Sakabe M, Tsuneda T, Sugao M, Iwamoto J, Nagasawa H, Inoue H. Bradycardia-dependent ECG changes in Brugada syndrome. *Circ J.* 2006;70:896–901.
45. Kamakura S, Ohe T, Nakazawa K, Aizawa Y, Shimizu A, Horie M, Ogawa S, Okumura K, Tsuchihashi K, Sugi K, Makita N, Hagiwara N, Inoue H, Atarashi H, Aihara N, Shimizu W, Kurita T, Suyama K, Noda T, Satomi K, Okamura H, Tomoike H. Long-term prognosis of probands with Brugada-pattern ST elevation in V1–V3 leads. *Circ Arrhythmia Electrophysiol.* 2009;2:495–503.
46. Takagi M, Aihara N, Takaki H, Taguchi A, Shimizu W, Kurita T, Suyama K, Kamakura S. Clinical characteristics of patients with spontaneous or inducible ventricular fibrillation without apparent heart disease presenting with J wave and ST segment elevation in inferior leads. *J Cardiovasc Electrophysiol.* 2000;11:844–848.

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.

Available online at www.sciencedirect.com

SciVerse ScienceDirect

Journal of Electrocardiology 44 (2011) 736–741

JOURNAL OF Electrocardiology

www.jecgonline.com

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

Takashi Kurita, MD, PhD,[a,*] Takashi Noda, MD, PhD,[b] Takeshi Aiba, MD, PhD,[b] Ikutaro Nakajima, MD,[b] Wataru Shimizu, MD, PhD,[b] Koichiro Motoki, MD, PhD,[a] Ryobun Yasuoka, MD, PhD,[a] Shunichi Miyazaki, MD, PhD,[a] Shiro Kamakura, MD, PhD[b]

[a]*Department of Medicine, Division of Cardiology, Faculty of Medicine, Kinki University, Osaka, Japan*

[b]*Division of Cardiology, National Cerebral and Cardiovascular Center, Osaka, Japan*

Received 14 April 2011

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 Ca^{2+} 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.

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 proarrhytmic 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

* Corresponding author. Department of Medicine, Division of Cardiology, Faculty of Medicine, Kinki University, 377-2 Ohono-Higashi, Osaka-Sayama, Osaka 589-8511, Japan.

E-mail address: kuritat@med.kindai.ac.jp

0022-0736/$ – see front matter © 2011 Elsevier Inc. All rights reserved.
doi:10.1016/j.jelectrocard.2011.09.002

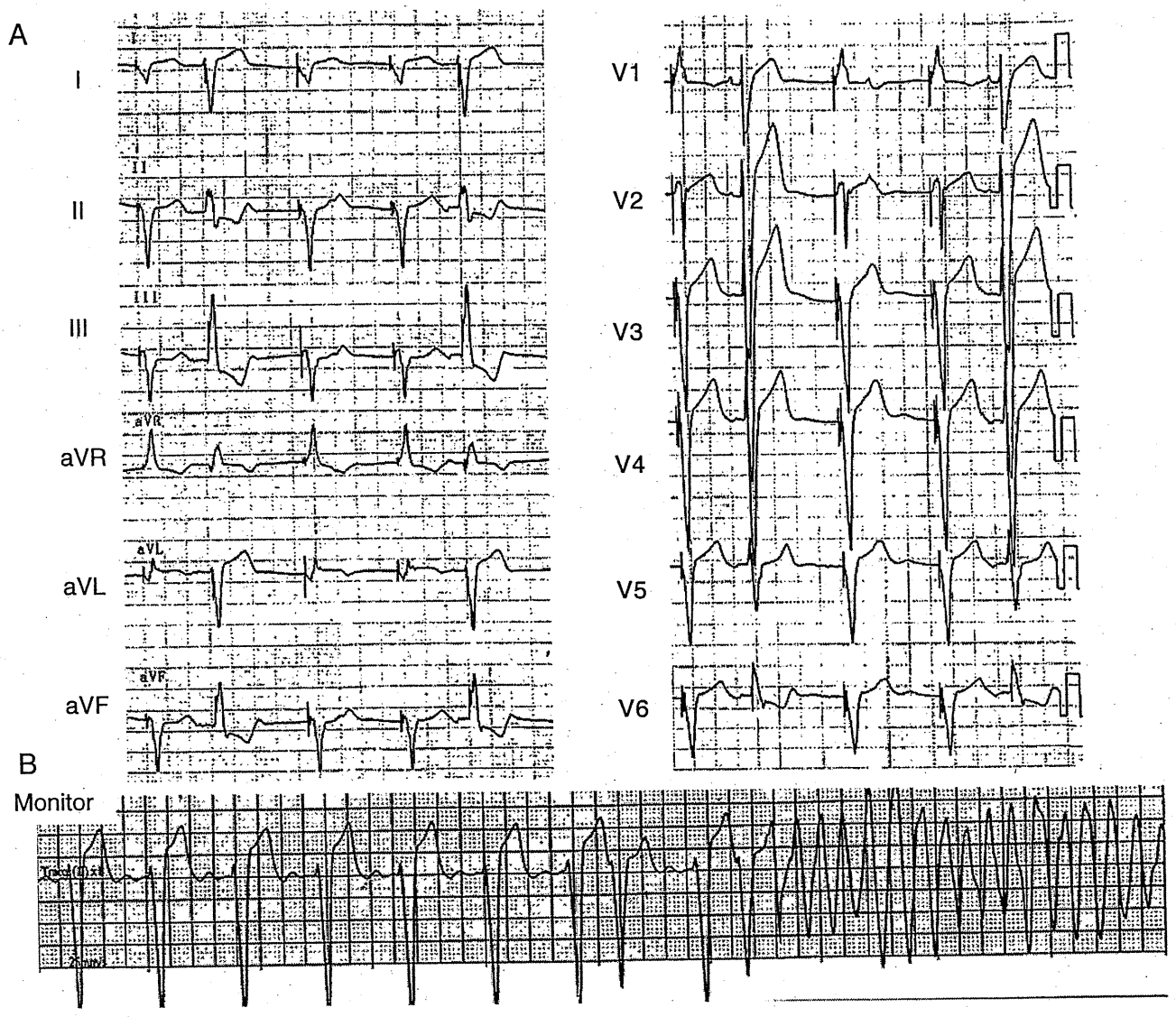

Fig. 1. A case with newly development of VF 6 days after implantation of CRT pacemaker (CRT-P). A, CRT-P was implanted in heart failure patient with CLBBB and permanent AF. Because of AF, occasional conducted QRS complexes with CLBBB configuration are seen. B, This patient had a long history (>20 years) 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

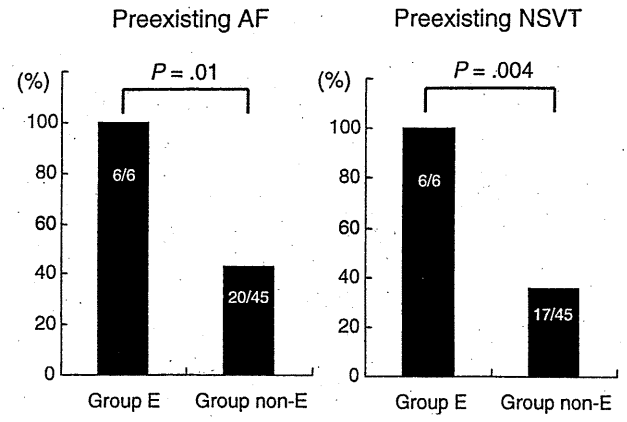

Fig. 2. Preexisting arrhythmias in the patients with (group E) and those without (group non-E) early development of lethal arrhythmic events after CRT. Preexisting AF and NSVT were observed more frequently in group E than group non-E (6/6 vs 19/45, $P < .01$, and 6/6 vs 17/45, $P < .01$, respectively).

may set a sage for reentry of excitation causing VT/VF. Spatially heterogenous 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 endocardia 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 al[19] 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

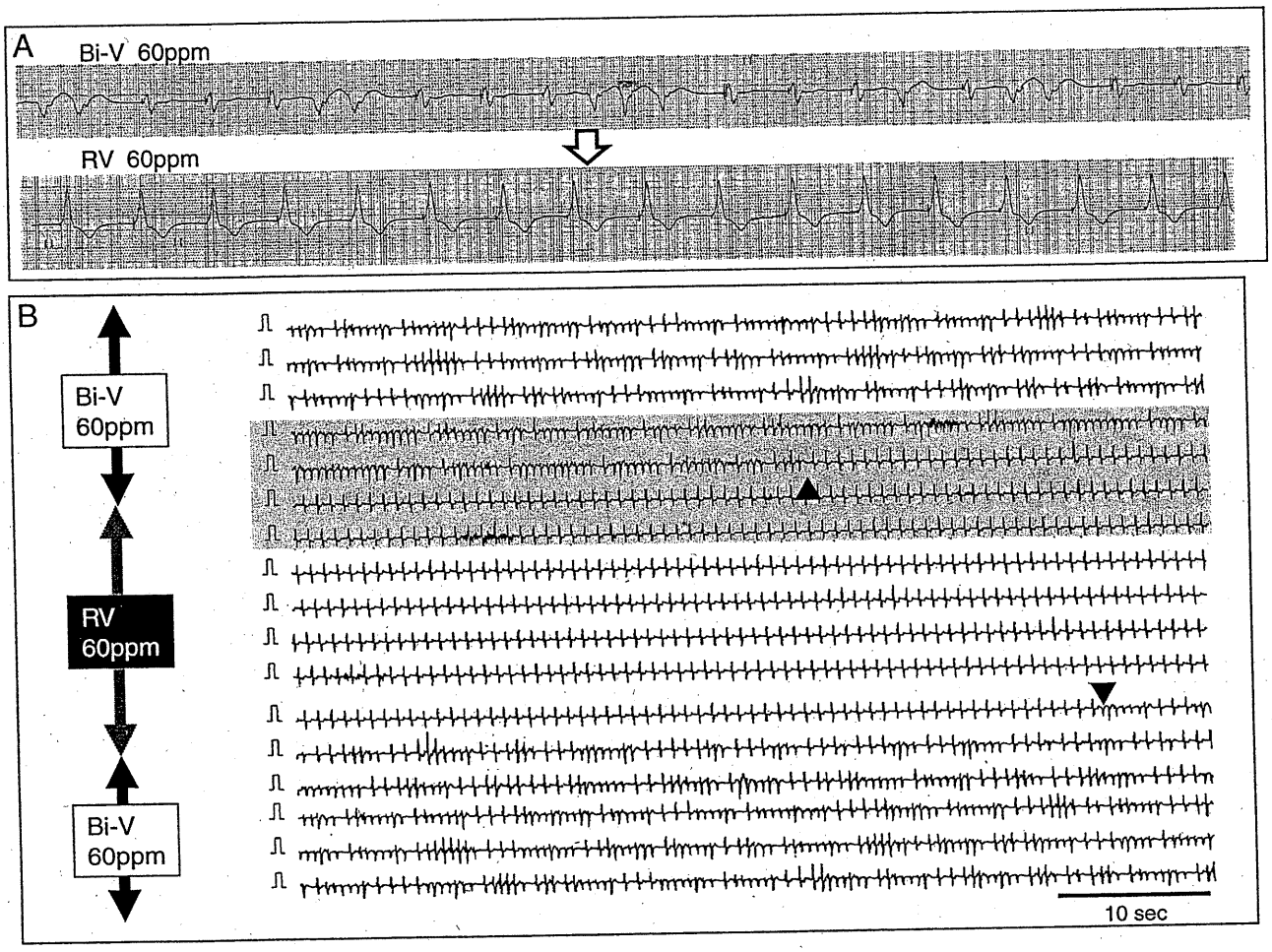

Fig. 3. Proarrhythmic effects of CRT in a patient of dilated cardiomyopathy (65-year-old man) with heart failure, complete AV block, and permanent AF. ICD had been implanted for the treatment of monomorphic sustained VT. Because of deterioration of heart failure, we upgraded from ICD to CRT-D. He responded 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 NHYA 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 or 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 al[29] 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 al[12] and Aiba and Tomaselli[13] have shown that CRT partially restores DHF-induced ion channel remodeling and abnormal Ca^{2+} homoeostasis 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 antiarryhthmic. 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 antiarrhtymic effects of CRT have come to be explained by the viewpoint of the ionic and genetic regulation of the myocytes.

References

1. Strickberger SA, Conti J, Daoud EG, et al. Patient election for cardiac resynchronization therapy. Circulation 2005;111:2146.
2. Sutton MG, Plappert T, Hilpisch KE, Abraham WT, Hayes DL, Chinchoy E. Sustained reverse left ventricular structural remodeling with cardiac resynchronization at one year is a function of etiology. Quantitative Doppler echocardiographic evidence from the Multicenter InSync Randomized Clinical Evaluation (MIRACLE). Circulation 2006;113:266.
3. Bradley DJ, Bradley EA, Baughman KL. Cardiac resynchronization and death from progressive heart failure. A meta-analysis of randomized controlled trials. JAMA 2003;289:730.
4. Bristow MR, Saxon LA, Boehmer J. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med 2004;350:2140.
5. Cleland JGF, Daubert JC, Erdmann E. for the Cardiac Resynchronization–Heart Failure (CARE-HF) Study Investigators. The effect of cardiac resynchronization therapy on morbidity and mortality in heart failure. N Engl J Med 2005;352:1539.
6. Cleland JG, Daubert JC, Erdmann E, et al. Longer-term effects of cardiac resynchronization therapy on mortality in heart failure [the CArdiac Resynchronization–Heart Failure (CARE-HF) trial extension phase]. Eur Heart J 2006;27:1928.
7. Medina-Ravell VA, Lankipalli RS, Yan GX. Effect of epicardial or biventricular pacing to prolong QT interval and increase transmural dispersion of repolarization. Does resynchronization therapy pose a risk for patients predisposed to long QT or torsade de pointes. Circulation 2003;107:740.
8. Fish JM, Di Diego JM, Nesterenko V, Antzelevich C. Epicardial activation of the left ventricular wall prolongs QT interval and transmural dispersion of repolarization. Implications for biventricular pacing. Circulation 2004;109:2136.
9. Turitto G, El-Sherif. Cardiac resynchronization therapy: a review of proarrhythmic and antiarrhythmic mechanisms. PACE 2007;30:115.
10. Nakajima I, Noda T, Shimizu W, et al. Cardio rhythm: related factors of early development of lethal arrhythmic events after cardiac resynchronization therapy. Europace 2011;13(suppl 1):i42.
11. Cazeau S, Leclercq C, Lavergne T, et al. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. N Engl J Med 2001;344:873.
12. Aiba T, Hesketh GG, Barth AS, et al. Electrophysiological consequences of dyssynchronous heart failure and its restoration by resynchronization therapy. Circulation 2009;119:1220.
13. Aiba T, Tomaselli GF. Electrical remodeling in the failing heart. Curr Opin Cardiol 2010;25:29 Review.
14. Fröhlich G, Steffel J, Hürlimann D, et al. Upgrading to resynchronization therapy after chronic right ventricular pacing improves left ventricular remodelling. Eur Heart J 2010;31:1477.
15. Ikutomi M, Matsusita M, Arashi H, et al. Effects of cardiac resynchronization therapy on the arrhythmic substrate in a 1 patient with long QT and torsades de pointes. J Arhythmia 2011 [in press].
16. Cranefield PF, Hoffman BF. Reentry: slow conduction, summation and inhibition. Circulation 1971;44:309.
17. Spach MS. Anisotropic structural complexities in the genesis of reentrant arrhythmias. Circulation 1991;84:1447.
18. Bordachar P, Derval N, Ploux S, et al. Left ventricular endocardial stimulation for severe heart failure. J Am Coll Cardiol 2010;56:747.
19. Tanabe Y, Chinushi M, Washizuka T, et al. Suppression of electrical storm by biventricular pacing in a patient with idiopathic dilated cardiomyopathy and ventricular tachycardia. Pacing Clin Electrophysiol 2003;26(Pt 1):101.
20. McSwain RL, Schwartz RA, DeLurgio DB, Mera FV, Langberg JJ, Leon AR. The impact of cardiac resynchronization therapy on ventricular tachycardia/fibrillation: an analysis from the combined Contak-CD and InSync-ICD studies. J Cardiovasc Electrophysiol 2005;16:1168.
21. Higgins SL, Yong P, Sheck D. Biventricular pacing diminishes the need for implantable cardioverter defibrillator therapy: Ventak CHF Investigators. J Am Coll Cardiol 2000;36:824.
22. Arya A, Haghjoo M, Dehghani MR, Alasti M, Kazemi B, Sadr-Ameli MA. Effect of cardiac resynchronization therapy on the incidence of ventricular arrhythmias in patients with an implantable cardioverter-defibrillator. Heart Rhythm 2005;2:1094.
23. Garrigue S, Barold SS, Hocini M, Jais P, Haissaguerre M, Clementy J. Treatment of drug refractory ventricular tachycardia by biventricular pacing. Pacing Clin Electrophysiol 2000;23:1700.
24. Maisel WH, Stevenson LW. Atrial fibrillation in heart failure: epidemiology, pathophysiology, and rationale for therapy. Am J Cardiol 2003;91(Suppl):2D.
25. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. Circulation 1998;98:946.
26. Dries DL, Exner DV, Gersh BJ, Domanski MJ, Waclawiw MA, Stevenson LV. A trial fibrillation is associated with an increased risk for mortality and heart failure progression in patients with

asymptomatic and symptomatic left ventricular systolic dysfunction: a retrospective analysis of the SOLVD trials. Studies of Left Ventricular Dysfunction. J Am Coll Cardiol 1998;32:695.
27. Middlekauff HR, Stevenson WG, Stevenson LW. Prognostic significance of atrial fibrillation in advanced heart failure: a study of 390 patients. Circulation 1991;84:40.
28. The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure: results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med 1987;316:1429.
29. Delnoy PPHM, Ottervanger JP, Luttikhuis HO, et al. Comparison of usefulness of cardiac resynchronization therapy in patients with atrial fibrillation and heart failure versus patients with sinus rhythm and heart failure. Am J Cardiol 2007;99:1252.
30. Tsuji Y, Zicha S, Qi XY, Kodama I, Nattel S. Potassium channel subunit remodeling in rabbits exposed to long-term bradycardia or tachycardia: discrete arrhythmogenic consequences related to differential delayed-rectifier changes. Circulation 2006;24:345.
31. Pu J, Boyden PA. Alterations of Na+ currents in myocytes from epicardial border zone of the infarcted heart. A possible ionic mechanism for reduced excitability and post repolarization refractoriness. Circ Res 1997;81:110.
32. Chakir K, Daya SK, Aiba T, et al. Mechanisms of enhanced beta-adrenergic reserve from cardiac resynchronization therapy. Circulation 2009;119:1231.

INTERNAL MEDICINE

□ CASE REPORT □

Incessant Monomorphic Ventricular Tachycardia Induced by the Proarrhythmic Effect of Amiodarone

Hisaki Makimoto, Takashi Noda, Takashi Kurita, Ikutaro Nakajima, Teruki Yokoyama, Atsushi Doi, Yuko Yamada, Hideo Okamura, Kazuhiro Satomi, Takeshi Aiba, Wataru Shimizu, Kazuhiro Suyama, Naohiko Aihara and Shiro Kamakura

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

(Intern Med 50: 2591-2595, 2011)
(DOI: 10.2169/internalmedicine.50.5588)

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

Division of Arrhythmia and Electrophysiology, Department of Cardiovascular Medicine, National Cerebral and Cardiovascular Center, Japan
Received for publication April 1, 2011; Accepted for publication July 22, 2011
Correspondence to Dr. Takashi Noda, tnoda@hsp.ncvc.go.jp

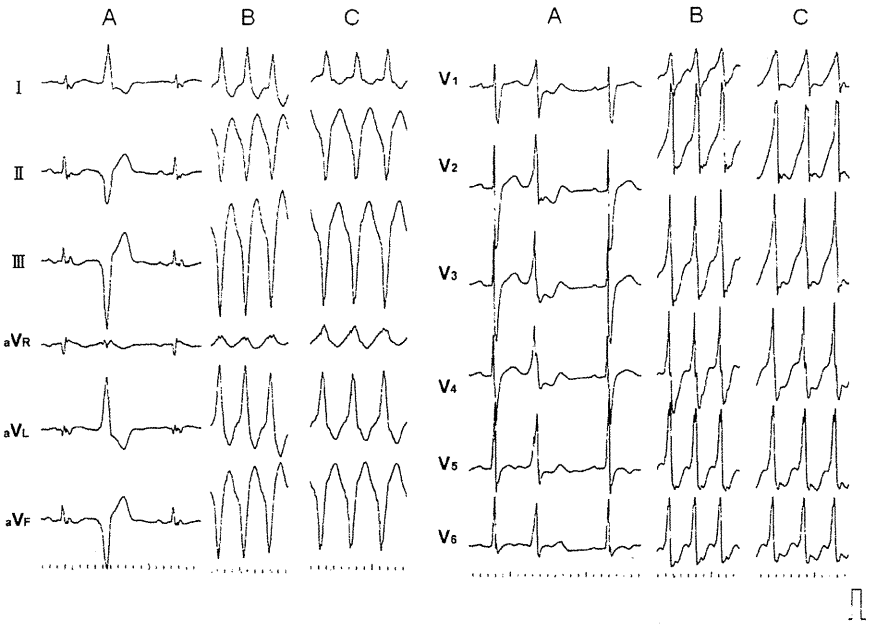

Figure 1. Twelve-lead electrocardiograms (ECGs) on admission and during ventricular tachycardia (VT) before and after amiodarone. The ECG showed sinus rhythm of 84 beats per minute with first degree atrio-ventricular block, and occasional premature ventricular complexes (PVC) (A). Before amiodarone administration, 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-