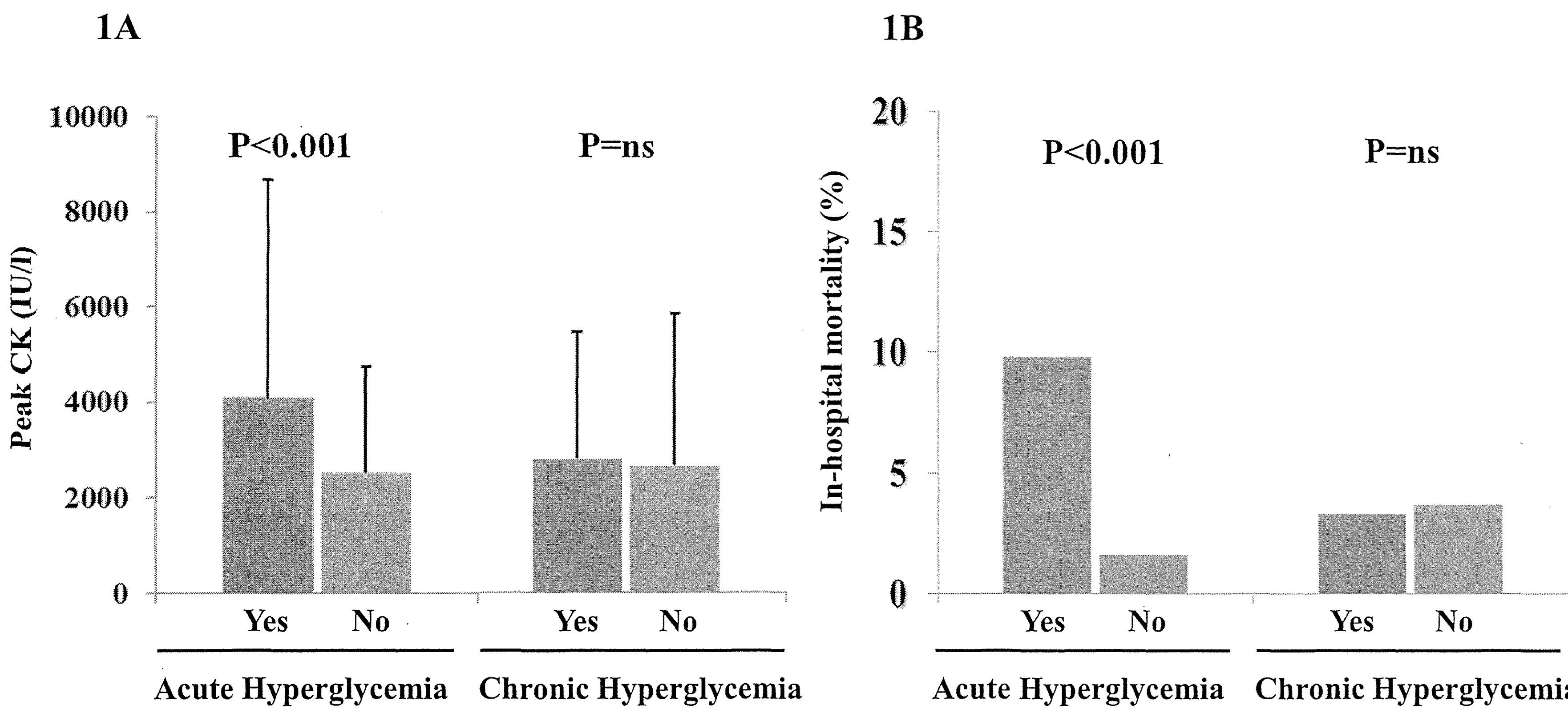
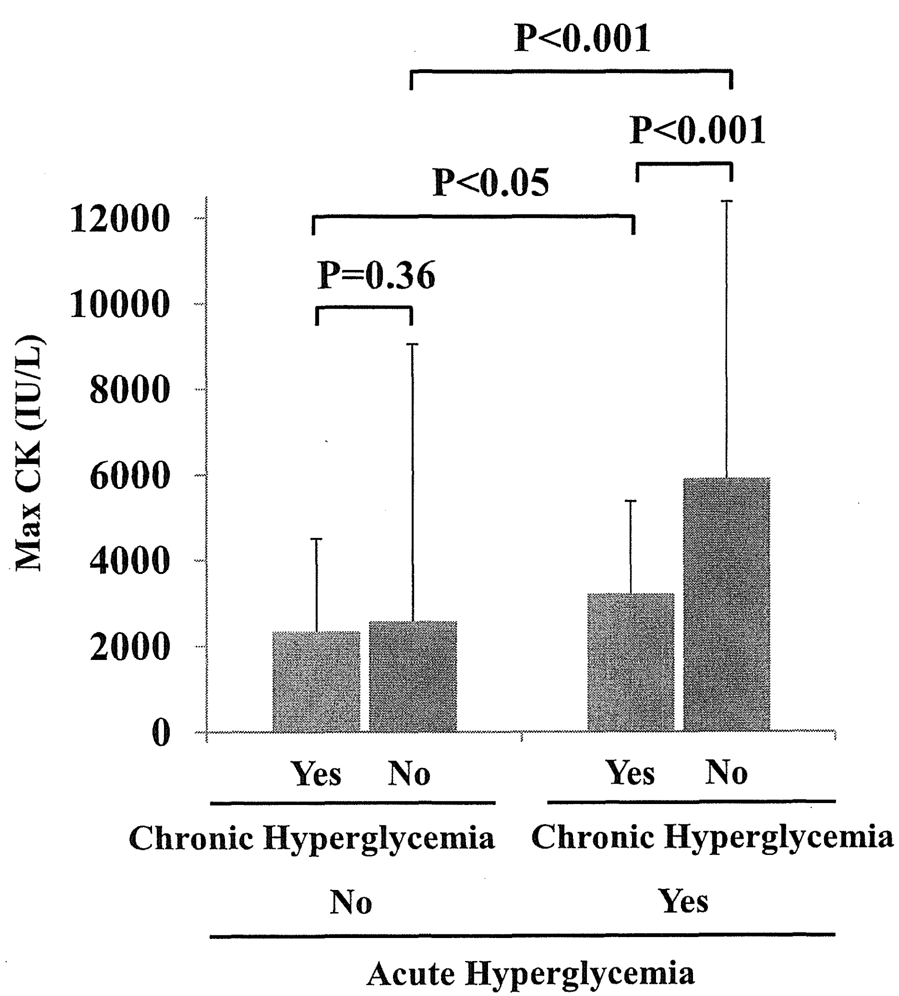
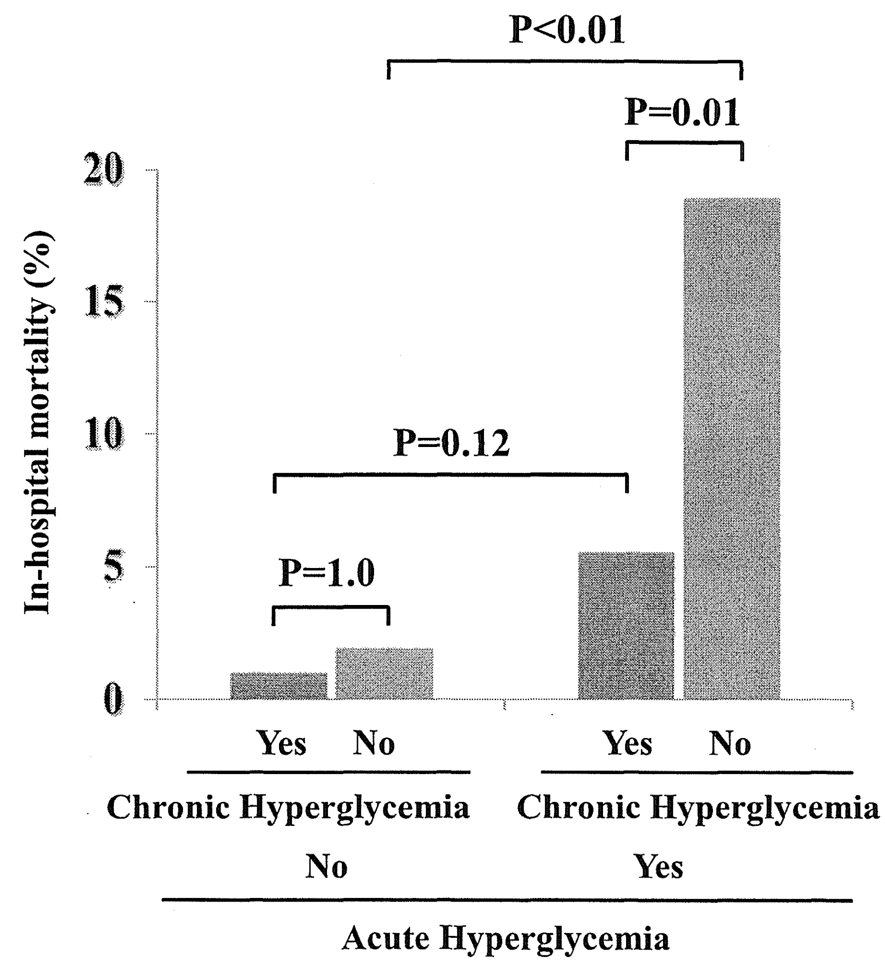
Table 2
Baseline characteristics of patients with and without chronic hyperglycemia

Variables	Chronic Hyperglycemia		pValue
	Yes (n=212)	No (n=484)	
Age (yrs)	68.6±12.4	67.3±12.7	0.192
Men	74%	71%	0.583
Body mass index (kg/m^2)	24.4±3.9	23.2±3.7	<0.001
Diabetes Mellitus	83%	13%	<0.001
Hypertension	73%	65%	0.065
Dyslipidemia	62%	53%	0.031
Smoker	34%	32%	0.736
Chronic kidney disease	36%	32%	0.296
Previous myocardial infarction	8%	10%	0.491
ST elevation myocardial infarction	80%	84%	0.229
Anterior location	36%	41%	0.238
Killip class 2 to 4	20%	19%	0.754
Elapsed time (hour)	8.1±10.3	7.1±9.6	0.206
Primary percutaneous coronary intervention	88%	87%	0.711
Medication before infarction			
Antiplatelet agent	20%	18%	0.600
Angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers	31%	21%	0.007
Calcium-channel blocker	27%	26%	0.926
Beta-blocker	10%	11%	1.000
Statin	22%	18%	0.090
Oral hypoglycemic agent	35%	4%	<0.001
Insulin	9%	1%	<0.001


1A
1B
Peak CK (IU/l)
10000
8000
6000
4000
2000
0
P<0.001
P=ns
Yes
No
Yes
No
Acute Hyperglycemia
Chronic Hyperglycemia
In-hospital mortality (%)
20
15
10
5
0
P<0.001
P=ns
Yes
No
Yes
No
Acute Hyperglycemia
Chronic Hyperglycemia



P<0.001
P<0.001
P<0.05
P=0.36
Max CK (IU/L)
12000
10000
8000
6000
4000
2000
0
Yes
No
Yes
No
Chronic Hyperglycemia
Chronic Hyperglycemia
No
Yes
Acute Hyperglycemia



P<0.01
P=0.01
P=0.12
P=1.0
In-hospital mortality (%)
20
15
10
5
0
Yes
No
Yes
No
Chronic Hyperglycemia
Chronic Hyperglycemia
No
Yes
Acute Hyperglycemia

- Acute hyperglycemia is associated with large infarct size and high in-hospital mortality in patients with AMI.
- Infarct size and in-hospital mortality are not different between patients with chronic hyperglycemia and those without.
- Paradoxically, chronic hyperglycemia may abate the adverse effects of acute hyperglycemia.

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IMAGES IN CARDIOVASCULAR MEDICINE

Non-Contrast T1-Weighted Magnetic Resonance Imaging at 3.0 Tesla in a Patient Undergoing Elective Percutaneous Coronary Intervention

– Clinical and Pathological Significance of High-Intensity Plaque –

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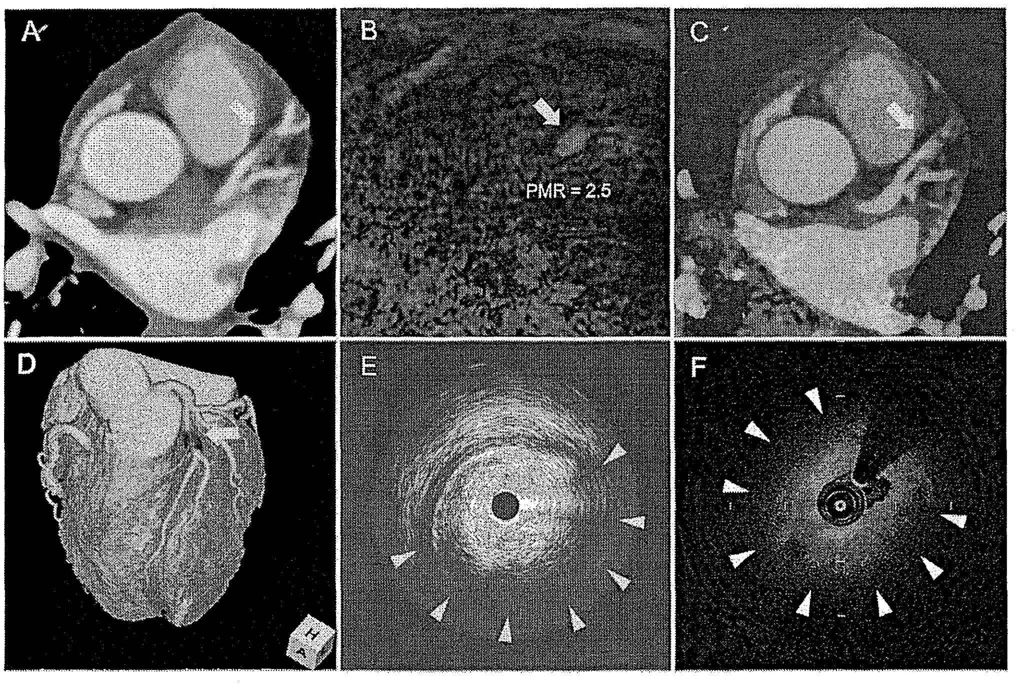

Figure 1. Computed tomography angiography (CTA) and magnetic resonance imaging of the coronary artery prior to percutaneous coronary intervention. (A) Coronary CTA showing a lesion of the left anterior descending artery (LAD) with significant stenosis and positive vessel remodeling (yellow arrow). (B) Non-contrast T1-weighted magnetic resonance imaging (T1WI) at 3.0 T showing a high-intensity plaque with a plaque-to-myocardium signal intensity ratio (PMR) of 2.5 in a LAD lesion, which corresponds to a coronary plaque detected on CTA (yellow arrow). (C) Two-dimensional fusion image between coronary CTA and non-contrast T1WI at 3.0 T (Ziostation 2; Ziosoft, Tokyo, Japan). (D) Three-dimensional fusion image between coronary CTA (volume-rendered image) and non-contrast T1WI at 3.0 T. (E) Intravascular ultrasound (View It, Terumo, Tokyo, Japan) showing the heterogeneous appearance of a large intimal plaque and low-echogenicity region in the deeper intima with remarkable attenuation (yellow arrowheads). (F) Optical coherence tomography (ILUMIEN OPTIS, St. Jude Medical Japan, Tokyo, Japan) showing an extensive signal-poor region with low backscattering and a lipid arc of 286° (white arrowheads).

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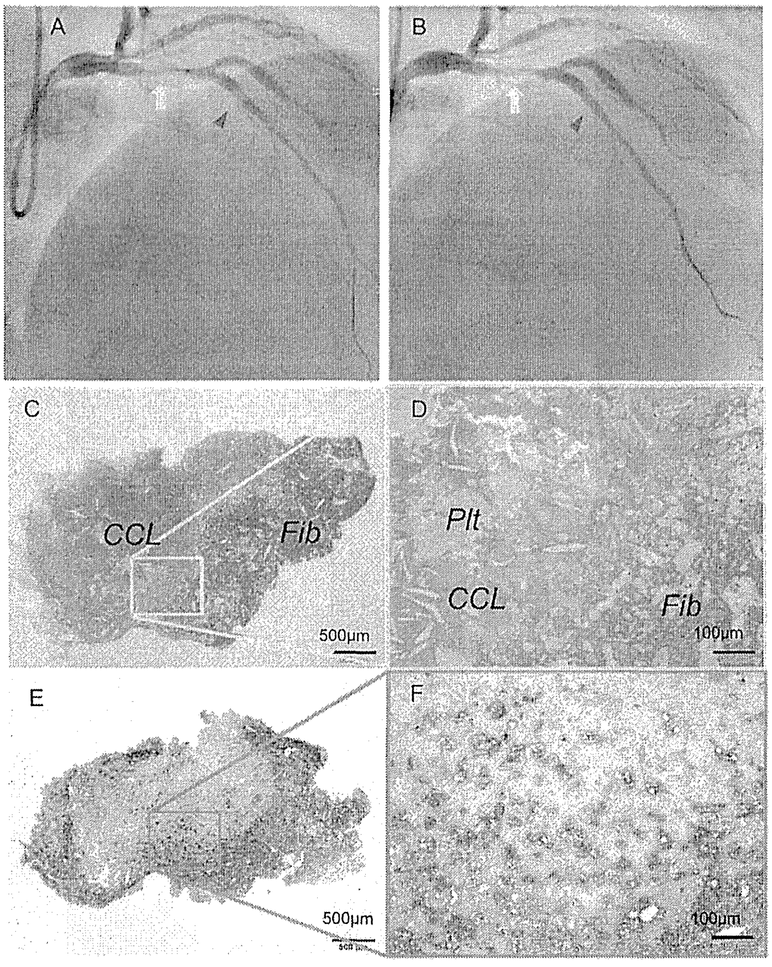

Figure 2. Coronary angiography during percutaneous coronary intervention and microscopy of the specimen aspirated from the target vessel. (A) Coronary angiography immediately after pre-dilatation at the target lesion (yellow arrow) showing a filling defect in the distal segment of the left anterior descending artery (red arrowhead). (B) The filling defect disappeared after intra-coronary aspiration (red arrowhead). (C) Low- and (D) high-magnification microscopy of the aspirated specimen showing an acute thrombus containing a large amount of the necrotic core with numerous cholesterol clefts (CCL), fibrin (Fib), and platelets (Plt) (H&E). (E) Low- and (F) high-magnification immunohistochemistry indicating extensive infiltration of $CD68^+$ macrophages within the necrotic core and thrombus.

Vulnerable or high-risk atherosclerotic plaque is prone to rupture and to thus cause acute coronary syndrome, but detecting this plaque on coronary plaque imaging has been challenging.[1] In previous studies we described the characteristics of coronary high-intensity plaque (HIP) on non-contrast T1-weighted magnetic resonance imaging (T1WI),[2,3] and showed that this plaque was associated with the slow- or no-reflow phenomenon and with periprocedural myocardial injuries during elective percutaneous coronary intervention (PCI), as well as with future coronary events.[2,4,5] High-spatial-resolution 3.0-T magnetic resonance imaging (MRI) of carotid plaques had substantial improvement in imaging quality and signal-to-noise and contrast-to-noise ratios compared with 1.5-T MRI.[6] Few studies, however, have involved coronary plaque imaging using non-contrast T1WI with 3.0-T clinical MRI.

In a 46-year-old man with stable effort angina pectoris, coronary computed tomography angiography showed significant stenosis with a low-density coronary plaque and positive vessel remodeling in the proximal portion of the left anterior descending artery (LAD; **Figure 1A**; **Movie S1**). Non-contrast T1WI was done on 3.0-T MRI with a 32-channel cardiac coil (MAGNETOM Verio; Siemens AG Healthcare Sector, Erlangen, Germany). Coronary plaque imaging was performed using an inversion recovery-prepared 3-D T1W turbo fast low-angle shot sequence with an electrocardiographic trigger, navigator-gated free-breathing, and fat suppression, with transaxial sections covering the whole heart (inversion time, 650 ms; field of view, 280×228 mm; acquisition matrix, 256×187; reconstruction matrix, 512×374; acquisition slice thickness, 1.0 mm; reconstruction spatial resolution, 0.6×0.5×0.6 mm; repetition time/echo, 4.7 ms/2.13 ms; flip angle, 12°; GRAPP factor, 2; navigator gating window, ±1.5–2.5 mm; and data acquisition window, 84–120 ms). The trigger delay and acquisition window were set based on the period of minimal right coronary artery motion as determined on cine-MRI.[5] Acquisition time and navigation efficiency in this case were 15 min and 35%, respectively. The plaque-to-myocardium signal intensity ratio, defined as the signal intensity of the coronary plaque divided by that of the nearby left ventricular myocardium, was calculated to be 2.5 (**Figure 1B**; **Movie S2**). Intravascular ultrasound showed a large intimal plaque and a region of low echogenicity that had remarkable attenuation (**Figure 1E**). Optical CT showed an extensive signal-poor region with low backscattering and a lipid arc of 286° (**Figure 1F**). The patient underwent elective PCI for proximal LAD lesion. Following the first balloon dilatation, a filling defect was observed in the distal segment of the LAD and the slow-flow phenomenon developed (**Figure 2A**); this defect disappeared following intra-coronary aspiration

(**Figure 2B**). Microscopy of the aspirated specimen showed a large amount of the necrotic core with overlying platelet- and fibrin-rich thrombus (**Figures 2C,D**). Immunohistology confirmed numerous $CD68^+$ macrophages within the aspirated specimen (**Figures 2E,F**), suggesting that the coronary embolus may have involved the large necrotic core with extensive inflammation.

In the present case, we successfully imaged coronary plaque defined as HIP on non-contrast T1WI using 3.0-T MRI. MRI was originally developed for carotid artery examinations but has emerged as a novel modality for atherosclerotic plaque characterization.[7] In particular, high-intensity signals observed in carotid plaque using inversion recovery-based 3-D T1WI have been found to be associated with recent ischemic cerebrovascular events and are related to the American Heart Association classification type VI complex plaque, which is characterized by luminal surface defects, intraplaque hemorrhage, thrombus, or calcified nodules.[7,8] Plaque imaging at 3.0 T is expected to provide improved imaging quality and better signal-to-noise and contrast-to-noise ratios compared with 1.5-T MRI. There have been few reports, however, of coronary artery imaging using 3.0-T MRI. Future studies comparing 1.5-T and 3.0-T MRI are warranted to assess coronary plaque.

Importantly, in this particular case, the coronary plaque defined as HIP on non-contrast T1WI at 3.0 T was associated with coronary embolus and slow flow following PCI. Specimens collected from the coronary artery contained atheroma with lipid-rich necrotic cores (**Figure 2**), consistent with MRI findings of hyperintense carotid plaque. Further studies are also needed to identify the plaque components of coronary HIP visualized on T1WI, and thus elucidate the mechanisms underlying acute coronary syndrome and the development of atherosclerosis.

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Supplementary Files

Supplementary File 1

Movie S1. Serial imaging of the heart with enhanced computed tomography angiography showing coronary plaque with severe stenosis, positive vessel remodeling, and low plaque density at the proximal portion of the left anterior descending artery (orange arrow).

Supplementary File 2

Movie S2. Serial imaging of the heart on non-contrast T1-weighted magnetic resonance imaging at 3.0 T showing a high-intensity plaque at the proximal left anterior descending artery (orange arrow), corresponding with the lesion detected on computed tomography angiography.

Please find supplementary file(s);
http://dx.doi.org/10.1253/circj.CJ-14-0897

Original Article

Electrical Storm in Patients With Brugada Syndrome Is Associated With Early Repolarization

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Background—Electrical storms (ESs) in patients with Brugada syndrome (BrS) are rare though potentially lethal.

Methods and Results—We studied 22 men with BrS and ES, defined as ≥3 episodes/d of ventricular fibrillation (VF) and compared their characteristics with those of 110 age-matched, control men with BrS without ES. BrS was diagnosed by a spontaneous or drug-induced type 1 pattern on the ECG in the absence of structural heart disease. Early repolarization (ER) was diagnosed by J waves, ie, >0.1 mV notches or slurs of the terminal portion of the QRS complex. The BrS ECG pattern was provoked with pilsicainide. A spontaneous type I ECG pattern, J waves, and horizontal/descending ST elevation were found, respectively, in 77%, 36%, and 88% of patients with ES, versus 28% (*P*<0.0001), 9% (*P*=0.003), and 60% (*P*=0.06) of controls. The J-wave amplitude was significantly higher in patients with than without ES (*P*=0.03). VF occurred during undisturbed sinus rhythm in 14 of 19 patients (74%), and ES were controlled by isoproterenol administration. All patients with ES received an implantable cardioverter defibrillator and over a 6.0±5.4 years follow-up, the prognosis of patients with ES was significantly worse than that of patients without ES. Bepridil was effective in preventing VF in 6 patients.

Conclusions—A high prevalence of ER was found in a subgroup of patients with BrS associated with ES. ES appeared to be suppressed by isoproterenol or quinidine, whereas bepridil and quinidine were effective in the long-term prevention of VF in the highest-risk patients. **(*Circ Arrhythm Electrophysiol.* 2014;7:1122-1128.)**

Key Words: bepridil ■ Brugada syndrome ■ electrocardiography ■ isoproterenol ■ ventricular fibrillation

Brugada syndrome (BrS), characterized by ST-segment and J-point elevation in the right precordial leads of the ECG in the absence of structural heart disease, is a cause of sudden cardiac death caused by ventricular fibrillation (VF).[1] Albeit rare, a subset of patients experiencing BrS develop potentially fatal storms of VF.[2–6] Their clinical characterization is important from the perspectives of risk stratification and development of new and effective therapies.

Clinical Perspective on p 1128

We recently observed a case of BrS characterized by prominent J waves in the inferolateral leads of the 12-lead ECG and electrical storms (ESs).[7] Case-control studies have described a close association between J waves, a sign of early repolarization (ER), and idiopathic VF.[8–10] The presence of J waves in patients presenting with BrS may also be a predictor of poor prognosis.[6,11–13] The purpose of this multicenter study was to evaluate the characteristics of patients with BrS and ES, with a special attention to the presence of J waves.

Methods

Study Population

We retrospectively identified 22 men at 8 Japanese medical institutions, who presented with BrS and ES, defined as ≥3 episodes of VF/d. BrS was diagnosed according to the following currently accepted criteria[2,6,11–14]: (1) ≥0.2 mV elevation of the J point with type 1 ST elevation in ≥1 right precordial lead(s) at baseline or after provocation with pilsicainide; (2) normal right and left ventricular

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size and function on chest radiograph and transthoracic echocardiography. Among these 22 patients, 4 had been included in previous studies.[2,6,12,14] Patients who had experienced a cardiac arrest or VF underwent provocation of coronary artery spasm with acetylcholine or ergonovine. We randomly chose 110 age-matched men presenting with BrS and no history of ES as controls and compared their clinical and ECG characteristics with those of the patients with ES.

This study complied with the guidelines of the Declaration of Helsinki and was approved by the institutional review board of Gunma University Hospital. All patients granted their written, informed consent to participate in this study.

ECG Analysis

The RR, PR QRS, QT, and corrected QT (using Bazett formula) intervals of the ECG were measured. An ER pattern was defined as the presence of a positive J wave, defined as a notch or slur at the terminal portion of the QRS complex, >0.1 mV in amplitude above the isoelectric line in ≥2 contiguous lead(s).[8–10] The J wave was classified as inferior if present in leads II, III, and aVF; left precordial if present in leads V4 to V6; and high lateral if present in leads I and aVL. Using the definitions of Tikkanen et al,[15] the ST-segment pattern after the J-point was classified as rapidly ascending/upsloping or horizontal/descending.

Data Analysis

The clinical characteristics, ECG intervals, J-wave prevalence and amplitude, and prevalence of spontaneous type 1 ECG pattern were compared in patients with versus without ES. When available, the ECG recorded during long-term follow-up were compared with those recorded at the time of ES, with special attention to the J waves. The patients' pharmacological and nonpharmacological therapy and long-term outcomes were recorded. The antiarrhythmic drug regimens were chosen according to each physician's preference and, if clinically ineffective, were replaced, in a trial and error manner.

Statistical Analysis

Continuous measurements are expressed as means±SD or medians and interquartile ranges, as appropriate, and categorical variables as counts and percentages. Differences between continuous variables were examined by the Mann-Whitney test, whereas categorical variables were compared by the Fisher exact test. We performed a logistic regression analysis in search of independent electrocardiographic predictors of arrhythmic risks, reported as odds ratio and 95% confidence intervals. The survivals were analyzed by the Kaplan-Meier method and compared using the log-rank test. The statistical analyses were performed with the Ekuseru-Toukei 2012 statistical software package (Social Survey Research Information Co., Ltd). A P value <0.05 was considered statistically significant.

Results

Patients With VF Storm

The characteristics of 22 men with BrS and VF storms are shown in Table 1. ES was the first episode of VF in 16 patients, while it occurred 3.2±2.4 years after implantation of cardioverter defibrillators (ICD) in the other 6 patients. A spontaneous type 1 ECG pattern was observed in 17 patients, and a pilsicainide provocation test was needed in the remaining 5 patients. Acetylcholine or ergonovine excluded the diagnosis of vasospastic angina in 9 of 9 patients who underwent provocation tests. VF was inducible in 6 of the 11 patients who underwent programmed ventricular stimulation to confirm the presence of an arrhythmogenic substrate promoting the development of VF or ventricular tachycardia.

VF Storm Characteristics

A mean of 25.2±82.0 VF episodes occurred during the storms. VF occurred between 8:00 PM and 6:00 AM in 14 patients (64%), between 6:00 AM and 8:00 PM in 7 patients (32%), and during both time intervals in 1 patient (4%). No apparent precipitating factor was identified.

The mode of VF onset was identified in 19 patients (Figure 1) and occurred during undisturbed sinus rhythm in 14 (74%), after a short-long-short sequence in 4 (21%), and under both circumstances in 1 patient (5%). The mean coupling interval of the first VF-triggering premature ventricular complex was 329±63 ms, ranging between 280 and 420 ms. The mode of VF onset was undetermined in 3 patients.

ER was present as J waves in 8 of the 22 patients (36%). The J waves were in the inferior ECG leads in 4 (Figure 2A), inferior and left precordial leads in 2 (Figure 2B), and inferior, left precordial and high lateral leads in 2 patients. A prominent accentuation of the J wave immediately before the onset of VF (Figures 3) was observed in 2 patients. The ST-segment pattern in patients with ES and J waves was rapidly ascending/upsloping in 1 (13%) and horizontal/descending in 7 patients (87%). VF during ES developed during undisturbed sinus rhythm in 6 patients with versus 9 patients without ER, and after a short-long-short sequence in 3 patients with versus 2 patients without ER; the presence of ER did not influence the mode of VF onset during ES (P=0.40). The coupling interval of the first VF-triggering premature ventricular complex in patients with (350[94]) versus without (301[130]) J waves, was similar (P=0.54).

Short-Term Management of VF

All episodes of VF were terminated by external defibrillation or by an ICD. Overdrive pacing, left cardiac sympathetic block combined with atropine, and oral disopyramide were effective in 1 patient each. Thereafter, intravenous isoproterenol became the therapy of choice and effectively suppressed ES in the last 7 patients, combined with quinidine in 1 patient. Lidocaine, magnesium sulfate, propranolol, and mexiletine were ineffective in 4, 3, 2, and 1 patients, respectively. VF-triggering premature ventricular complexes originating from the right ventricular outflow tract were successfully eliminated by catheter ablation in 1 patient. In the other 12 patients, ES resolved spontaneously within 6 to 12 hours.

Comparisons of Patients With Versus Without ES

The characteristics of 22 men with BrS and ES versus 110 men with BrS and no ES are shown in Table 2. Among the 110 control men, 17 experienced a single VF episode, 13 experienced ≥1 syncopal episode(s), and 80 patients were asymptomatic. BrS was diagnosed by the presence of a spontaneous type 1 ECG pattern in 31 patients (28%) without ES, in contrast with 17 (77%) among the 22 patients with ES (P<0.0001). In 79 patients without ES (72%), BrS was diagnosed by a pilsicainide provocation test.

J waves >0.1 mV were observed in 10 of 110 patients without ES (9%), in contrast with 8 of 22 patients with ES (36%), a statistically significant difference (P=0.003). The J-wave amplitude was higher in patients with ES than those without ES (P=0.03). The J waves in patients without ES were

Table 1. Characteristics of 22 Men With BrS and VF Storms

Patient	FH of BrS/SCD	Age, y	Hour of First VF	Mode of VF Onset	Suppression of VF	Drug Trials	PVS	LTT	ICD	Years of Follow-Up	VF Recurrence (Time to Recurrence)
1	–/+	49	10:00	Und	...	...	Positive	...	+	8.3	+ (2.3)
2	–/–	26	21:45	Und	Isoproterenol	Magnesium, lidocaine	Positive	...	+	3.8	...
3	–/–	42	3:00	Und	Pacing	Lidocaine/ amiodarone/ propofol	Negative	...	+	2.6	...
4	–/–	25	0:35	Unknown	...	...	Negative	...	+	1.6	+ (0.2)
5	–/+	21	1:00	Und	...	Lidocaine	Negative	...	+	2.2	+ (0.5)
6	–/+	0.5	All day	Und	LSD/atropine	Propofol/ magnesium/ mexiletine	Negative	...	+	14	...
7	–/–	36	6:15	Und/SLS	Isoproterenol	...	Positive	Bep*	+	1.6	+ (0.4)
8	–/–	61	15:40	Und	...	...	Positive	...	+	0.7	+ (0.3)
9	–/–	42	4:24	SLS	Isoproterenol	...	Positive	Bep*	+	13.5	+ (4.8)
10	–/–	51	11:00	SLS	Isoproterenol	Lidocaine/ magnesium	Not performed	...	+	10.5	+ (6)
11	–/–	39	0:00	Und	Isoproterenol/Q	...	Not performed	Bep*	+	2.2	+ (0.7)
12	–/–	29	4:00	Und	Isoproterenol	...	Positive	Q*	+	7.4	+(3.3)
13	–/–	27	11:00	SLS	...	Cilostazol, quinidine, demopamine, isoproterenol	Negative	DP	+	2.0	+ (0.1)
14	–/–	70	0:22	Und	Isoproterenol	...	Not performed	...	+	12.7	+(0.2)
15	–/–	29	2:47	Unknown	...	...	Not performed	Q*	+	12.9	+(0.3)
16	–/–	33	14:30	Unknown	...	...	Not performed	...	+	15.5	...
17	–/–	53	22:38	Und	...	...	Not performed	...	+	12.5	...
18	–/–	42	22:18	Und	...	...	Not performed	Bep*	+	5.5	...
19	–/–	38	3:22	Und	...	...	Not performed	Amio*	+	2.2	...
20	–/–	50	16:28	SLS	...	...	Not performed	Bep*	+	5.8	...
21	–/–	19	21:18	Und	...	...	Not performed	Bep*	+	1.3	...
22	–/–	42	1:43	Und	...	...	Not performed	...	+	2.4	...

Bep indicates bepridil; BrS, Brugada syndrome; DP, disopyramide; FH, family history; ICD, implantable cardioverter defibrillator; LSD, Left cardiac sympathetic denervation; LTT, long-term therapy; PVS, programmed ventricular stimulation; SCD, sudden cardiac death; SLS, short-long-short sequence; Und, Undisturbed sinus rhythm; and VF, ventricular fibrillation.

*No recurrence of VF on therapy.

Adapted from Ohgo et al,[2] Kawata et al,[6] and Kawata et al[14] with permission of the publisher. Copyright © 2007, 2013, 2012, respectively, Elsevier.

in the inferior leads in 7, inferior and left precordial leads in 1, and high lateral in 2 patients, whereas the J waves in patients with ES were in the inferior leads in 4, inferior and left precordial leads in 2, and in the inferior, left precordial and high lateral leads in 2 patients. The distribution of leads with J waves was similar in patients with versus without ES (P=0.08). In 10 patients without ES and with J waves, the ST segment was horizontal/descending in 4 (40%) and rapidly ascending/upsloping in 6 (60%) patients; the ST-segment pattern in patients with versus without ES was similar (P=0.06). Furthermore, in patients with a history of ≥1 episode of VF, the prevalence of J wave was 28% and that of spontaneous type I ST-segment elevation was 72% versus 8 (P=0.003) and 22% (P<0.0001), respectively, in patients without history of VF episodes. By multiple variable logistic regression analysis, spontaneous type I ST elevation independently predicted the development of VF (odds ratio, 4.375; 95% confidence interval, 1.6–12.0; P=0.004) and ES (odds ratio, 7.1; 95% confidence interval, 2.1–24.6; P=0.002). However, combined spontaneous type I ST elevation and (1) J waves or (2) J waves plus a horizontal or descending ST segment was not independently predictive. Among patients with any episode of VF, the prevalence of J waves and spontaneous type I ST elevation was 21% and 44%, respectively, in patients with versus 8% (P=0.18) and 31% (P=0.46) in patients without ES.

Clinical Outcomes

Among the 22 patients with BrS and ES, 16 underwent implantation of ICD after the ES had abated and 6 patients had already received an ICD when the ES developed. Over a follow-up (6.4±5.0 years), 12 patients experienced VF recurrences after the first ES, of whom 9 were untreated with antiarrhythmic

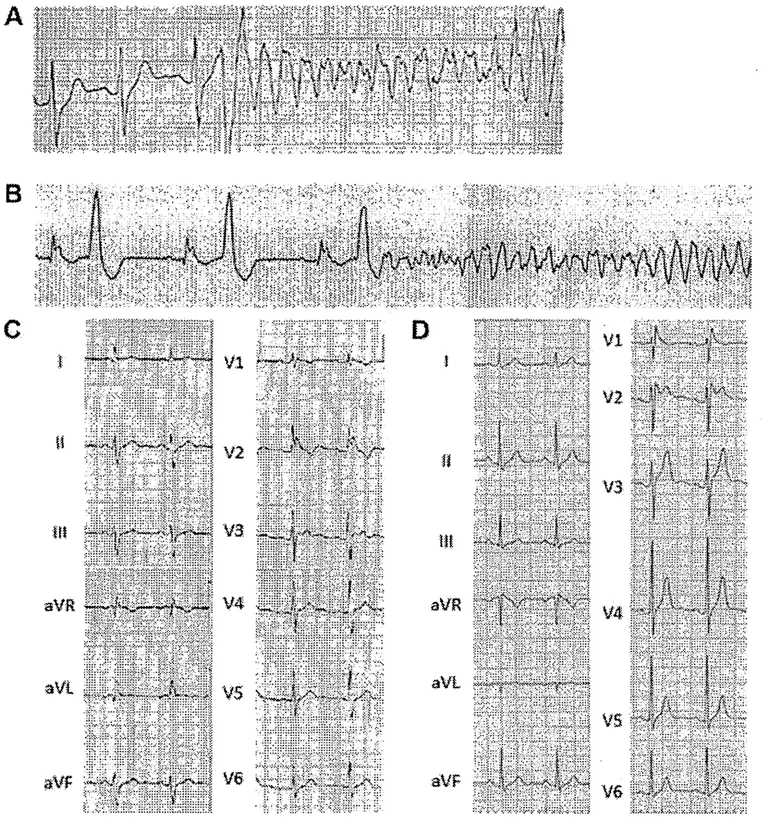

Figure 1. Onset of ventricular fibrillation (VF). **A,** VF developing during undisturbed sinus rhythm (patient no 3). **B,** VF following a short-long-short sequence with frequent premature ventricular complexes (patient no 10). **C** and **D,** J waves were absent during sinus rhythm on the 12-lead ECG of each patient.

drugs. However, 6 patients treated with bepridil, 100 to 200 mg daily, 2 patients treated with quinidine, 300 to 600 mg daily, and 1 patient treated with amiodarone, 100 mg daily, remained free from VF recurrences. One patient treated with disopyramide 300 mg daily experienced a single recurrence of VF. During follow-up, the J wave disappeared in 1, decreased in amplitude in 2 (Figure 3), and remained unchanged in 7 of 10 patients whose ECG were available during long-term follow-up.

ICD were implanted in 21 control patients, including 17 patients with histories of VF and 4 with histories of syncope. Quinidine was used for secondary prevention of VF in 1 patient. A single patient (5%) untreated with an antiarrhythmic drug experienced a recurrence of VF.

By Kaplan-Meier analysis of the cumulative incidence of recurrent arrhythmic events, the prognosis of patients with ES was significantly worse than that of patients without ES (Figure 4).

Discussion

The main finding of our study was a high prevalence of ER in patients presenting with BrS with versus without ES. Intravenous isoproterenol seemed effective in the short-term

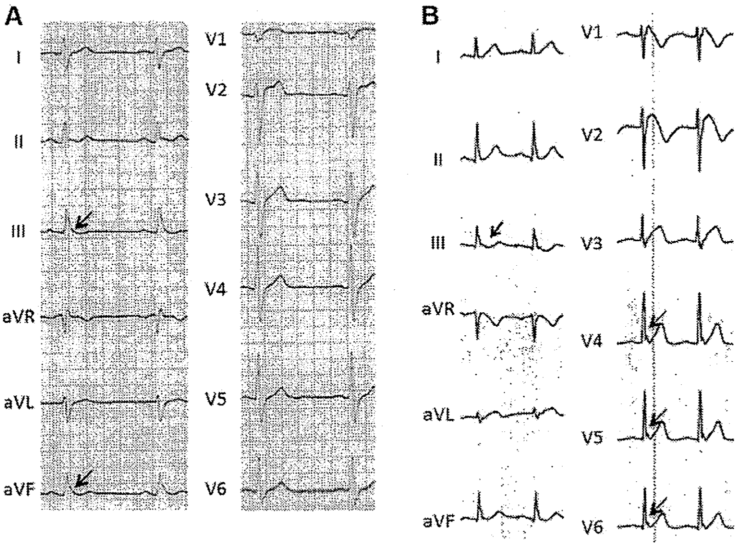

Figure 2. Twelve-lead ECG with J waves during sinus rhythm. **A,** J waves followed by horizontal/descending ST elevation are present in the inferior leads (arrows; patient no 14). **B,** J waves followed by rapidly ascending/upsloping ST elevation are visible in the inferolateral leads (patient no 7).

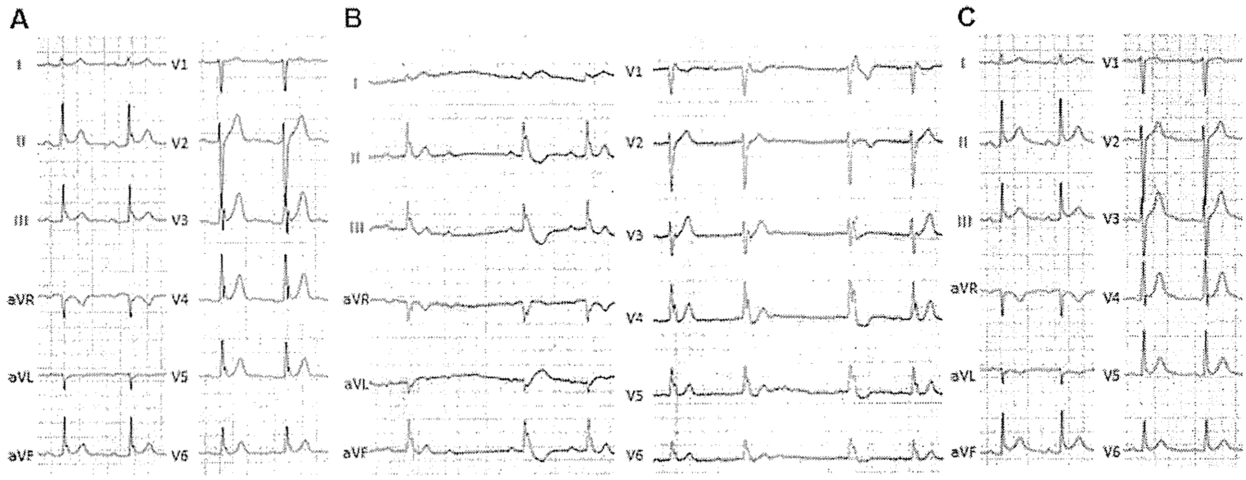

Figure 3. Accentuation of the J wave during electrical storm in patient no 13. **A**, 12-lead ECG recorded on admission before electrical storm (ES). J waves with a maximum amplitude of 0.5 mV were observed in leads I, II, III, aVF, and V3-V6. **B**, 12-lead ECG recorded before the second episode of VF on the same day. The J waves are more prominent than in (**A**). The pause-dependent augmentation is evident when the RR interval is lengthened by atrioventricular block. **C**, VF was well controlled by the infusion of isoproterenol. The amplitude of the J wave decreased in all leads. VF indicates ventricular fibrillation. Reprinted from Kaneko et al[7] with permission of the publisher. Copyright © 2012, Wiley Periodicals, Inc.

suppression of ES, while oral bepridil and quinidine effectively prevented long-term recurrences of VF. Patients with BrS and ER were at higher risk of ES and VF recurrences than patients without ER.

Regarding the ECG characteristics, patients with BrS and ES in this study had a higher prevalence of type 1 ECG pattern and J waves than the controls (Table 2). The prevalence of ER was also higher than reported in general Western populations[4,8,16,17] and in this country.[9,18] Therefore, the prevalence of J waves in patients with BrS and ES is higher than in (1) patients with BrS without ES,[12] and (2) the general population. Several studies have suggested that the presence of inferolateral J waves in BrS is associated with a higher risk of recurrent VF.[6,11–13] However, a relationship with ES in particular has not been described previously.

Studies in animals have suggested a common mechanism underlying (1) the ECG phenotype of BrS and (2) ER (the J wave) in idiopathic VF, both explained by a voltage gradient in the early phase of repolarization.[19] In BrS, the presence of a J wave in V1 to V3 is explained by a notched phase 1 of the right ventricular outflow tract myocardial action potential, which, when augmented, may be followed by a secondary dome resulting in a coved ST-T segment.[19,20] However, the pathophysiological mechanism(s) behind the ST-T changes observed in patients presenting with BrS remain(s) vigorously debated, and hypotheses have been formulated in favor of abnormalities of both depolarization and repolarization to explain the ECG phenotype of BrS.[21]

In patients with idiopathic VF, J waves are more prevalent in the inferior and lateral precordial leads and may be explained by a mechanism similar to that of the J waves observed in BrS.[19,20] They are augmented by an increased repolarization inhomogeneity from undetermined causes, along with the development of phase 2 reentry and subsequent VF. Although the ECG phenotype and response of VF to pharmaceuticals in BrS and J wave–associated idiopathic VF are similar, the J wave is only enhanced by class I antiarrhythmic drugs in BrS and not in J wave–associated idiopathic VF.[14] The presence of ER in BrS increases the risk of ES and recurrent VF[6,11–13] although the significance of the association between BrS and ER remains to be clarified.

A dissimilar mode of onset of VF has been reported in BrS–associated versus in J wave–associated idiopathic VF. In the study by Nam et al,[4] VF was triggered by a premature ventricular complex with a short-long-short sequence in 42 of 58 patients with ER (72.4%) versus 13 of 86 patients (15.1%) with BrS (P<0.01). Furthermore, the mean coupling interval of the VF-triggering premature ventricular complexes was significantly shorter in the group of patients presenting with idiopathic VF and ER than in patients presenting with BrS (P<0.01). In the present study, the mode of VF onset was known in 19 patients and developed during regular sinus rhythm in 14 patients (74%), after a short-long-short sequence in 4 (21%),

Table 2. Characteristics of 22 Men With BrS and ES vs 110 Men With BrS and No ES

	With ES	Without ES	P
Age, y	39 (23)	44 (18)	0.04
Family history of sudden death/BrS	3/0	12/3	0.47/0.58
Electrocardiographic intervals, ms			
RR	785 (212)	909 (213)	0.0005
PR	180 (26)	162 (24)	0.048
QRS	100 (29)	104 (16)	0.21
QT	340 (40)	396 (41)	<0.0001
QTc	390 (51)	394 (33)	0.02
Spontaneous type 1 ECG	17 (77)	31(28)	<0.0001
J wave >0.1 mV	8 (36)	10 (9)	0.003
J-wave amplitude, mV	0.3 (0.1)	0.2 (0.01)	0.03

Values are median (interquartile range) or numbers (%) of observations. BrS indicates Brugada syndrome; and ES, electrical storm.

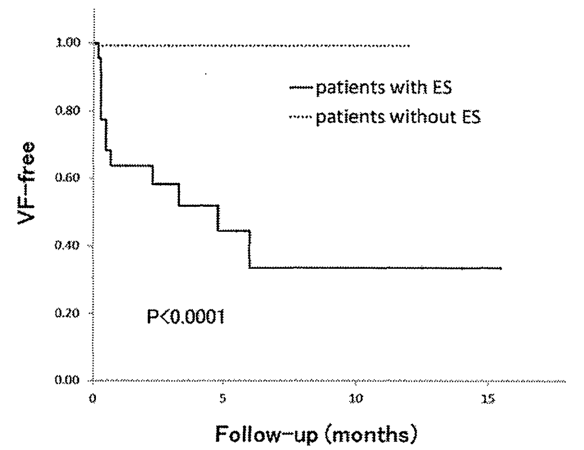

Figure 4. Kaplan-Meier estimates of ventricular fibrillation (VF) recurrence after electrical storms.

and in both circumstances in 1 patient (5%). Although the presence of ER did not influence the mode of onset of VF in the patients experiencing BrS complicated by ES, the role of ER in the development of VF is in need of further studies.

An association between (1) horizontal/descending ST elevation followed by ER and (2) an increased arrhythmic risk was recently observed in the general population[16] and in patients with histories of idiopathic VF.[17,22,23] Although we did not find a significantly higher prevalence of horizontal/descending ST elevation combined with ER in patients presenting with BrS and ES, a larger observational study is needed to clarify this point.

Intravenous isoproterenol or oral quinidine are the drugs of choice for the short-term management of ES in both BrS- and ER-associated idiopathic VF.[2–4] We found these drugs to be particularly effective in BrS with ER, presumably by augmenting the inward calcium currents, restoring the dome of the action potential, and mitigating the inhomogeneity of repolarization. Besides quinidine, bepridil, a class IV antiarrhythmic drug with Ito blocking properties, prevented VF in a small number of patients with BrS, although its long-term safety and efficacy was limited, especially in a severe form of BrS.[24–27] It is noteworthy that bepridil was effective in preventing VF storms on the long-term in the report of the largest number of patients presenting with BrS.[24–27]

Limitations of Our Study

The sample size of our study is small, although is the largest collected thus far. Furthermore, a genetic screen in search of a mutation could have contributed to (1) the identification of an arrhythmogenic cause and mechanism, and (2) providing insights into the therapy of this complication of BrS, although was not systematically performed.

Conclusions

In a subgroup of patients experiencing BrS with ER, a spontaneous type 1 ECG pattern was more prevalent than in similar patients without ER and seemed to incur a risk of ES and recurrent VF. Intravenous isoproterenol seemed effective in the short-term management of ES, while oral bepridil and quinidine prevented long-term recurrences of VF.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Electrical storms (ESs) in patients with Brugada syndrome (BrS), although rare, are potentially lethal. We compared the ECG characteristics of 22 men with BrS and ES, defined as ≥3 episodes/d of ventricular fibrillation, recruited at 8 Japanese medical centers, with those of 110 age-matched, control men with BrS without ES. We found a high prevalence of J waves in the group of patients with BrS complicated by ES. Specifically, a spontaneous type I ECG pattern and J waves and horizontal/descending ST elevation were present in 77%, 36%, and 88% of patients with ES, respectively, versus 28% (P<0.0001), 9% (P=0.003), and 60% (P=0.06) of controls, respectively. ES were suppressed by isoproterenol or quinidine. All patients with ES received an implantable cardioverter defibrillator and, over a follow-up of 6.6±5.3 years, the prognosis of patients with ES was significantly worse than that of patients without ES. Ventricular fibrillation was prevented on the long-term in 6 of 6 patients treated with bepridil. This is, to our knowledge, the largest study of patient presenting with BrS and ES. It underscores the significant association between the presence of J wave and ES in patients with BrS, and a high effectiveness of bepridil in the long-term prevention of ventricular fibrillation in the highest-risk patients with BrS.

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Electrical Storm in Patients With Brugada Syndrome Is Associated With Early Repolarization

Yoshiaki Kaneko, Minoru Horie, Shinichi Niwano, Kengo F. Kusano, Seiji Takatsuki, Takashi Kurita, Takeshi Mitsuhashi, Tadashi Nakajima, Tadanobu Irie, Kanae Hasegawa, Takashi Noda, Shiro Kamakura, Yoshiyasu Aizawa, Ryobun Yasuoka, Katsumi Torigoe, Hiroshi Suzuki, Toru Ohe, Akihiko Shimizu, Keiichi Fukuda, Masahiko Kurabayashi and Yoshifusa Aizawa

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Letter to the Editor

Reduction of myocardial inflammation with steroid is not necessarily associated with improvement in left ventricular function in patients with cardiac sarcoidosis: Predictors of functional improvement

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Cardiac sarcoidosis is rare but being increasingly recognized because of poor prognosis [1]. Steroids are the mainstay of treatment for cardiac sarcoidosis to resolve active myocardial inflammation [2,3]. Gallium-67 citrate (^{67}Ga) scintigraphy and ^{18}F-fluoro-2-deoxyglucose (FDG) positron emission tomography (PET) are used to evaluate the response to steroid treatment [4,5]. However, it remains unknown whether steroid treatment can completely resolve active myocardial inflammation evaluated by these imaging modalities and whether the resolution of inflammation is associated with an improvement in left ventricular (LV) function. The aim of this study was to determine the efficacy of steroid treatment for resolving inflammation and improving LV function and to elucidate predictors of the functional responder to steroid treatment in patients with cardiac sarcoidosis.

The study population consisted of 30 consecutive patients with cardiac sarcoidosis who had positive myocardial uptake of ^{67}Ga or ^{18}F-FDG at baseline between December 1994 and November 2012. ^{18}F-FDG PET was performed in 5 patients who had no positive myocardial uptake of ^{67}Ga, after patients were instructed to fast for at least 12 h, blood glucose level was determined to ensure a level of <150 mg/dl, and unfractionated heparin was administrated. Cardiac sarcoidosis was diagnosed on the basis of guidelines of the Japanese Ministry of Health and Welfare [6], and guidelines revised in 2006 by the Japan Society of Sarcoidosis and Other Granulomatous Disorders [7]. This study was performed according to the principles of the Declaration of Helsinki and was approved by the Institutional Ethics Committee.

Table 1
Clinical characteristics.

	All patients (n = 30)
Age (year)	61 ± 12
Female	20 (67)
Extracardiac organ involvement	
Lung	18 (60)
Skin	5 (17)
Eye	12 (40)
Other	6 (20)
Number of organ involvement	
1 site	6 (20)
2 sites	13 (43)
≥3 sites	11 (37)
NYHA functional class III or IV	10 (33)
LV end-diastolic volume (ml/m^2)	83 ± 19
LV end-systolic volume (ml/m^2)	49 ± 23
LV ejection fraction (%)	43 ± 15
High-degree heart block	13 (43)
Sustained ventricular tachycardia	12 (40)
Angiotensin-converting enzyme (IU/l)	14.9 ± 6.7
B-type natriuretic peptide (pg/ml)	361 ± 455
Initial dose of prednisone 30 mg/40 mg	27 (90)/3 (10)
Period of initial dose of prednisone (week)	5.6 ± 3.5
Maintenance dose of prednisone 5 to 7.5 mg/7.6 to 10 mg	16 (53)/14 (47)
Beta-blocker use	20 (67)
Cardiac resynchronization therapy	7 (23)

Data are presented as means ± standard deviation or numbers (%) of patients.
High-degree heart block includes complete atrioventricular block and Mobitz II block.
NYHA, New York Heart Association; LV, left ventricular.

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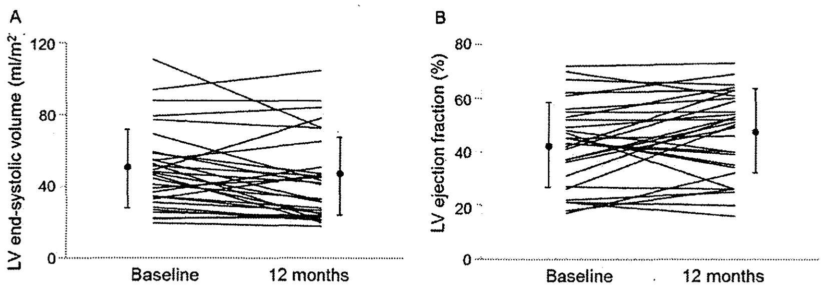

Fig. 1. Changes in LV end-systolic volume (A) and LV ejection fraction (B) after steroid treatment in the whole study population. LV, left ventricular.

All patients were treated with prednisone at an initial dose of 30 or 40 mg daily. Doses were tapered over a period of 6 to 12 months to a maintenance dose of 5 to 10 mg daily. ^{67}Ga scintigraphy or ^{18}F-FDG PET was repeated at a mean of 2 months after steroid treatment to evaluate the resolution of active myocardial inflammation. Echocardiography was repeated at a mean of 12 months after steroid treatment, and the functional responder to steroid treatment was defined as a patient who had ≥15% decrease in LV end-systolic volume [8].

Significant differences were analyzed using the *t* test and Mann-Whitney *U* test for continuous variables and the χ^2 test for categorical variables. Predictors of the functional responder to steroid treatment were assessed by univariate and multivariate analyses.

Clinical characteristics are summarized in Table 1. Multiple organ involvement was observed in 24 patients, and other 6 patients were classified as isolated cardiac sarcoidosis. All the 6 patients were diagnosed on the basis of histological confirmation on endomyocardial biopsy that identified non-caseating granuloma and inflammatory cell infiltration, but not necrosis or eosinophils.

After steroid treatment, positive myocardial uptake of ^{67}Ga or ^{18}F-FDG had completely disappeared in all patients. Echocardiography, however, showed that LV function did not improve in the whole study population (baseline vs. 12 months: 83 ± 19 ml/m^2 vs. 78 ± 23 ml/m^2; p = 0.280 for LV end-diastolic volume, 49 ± 23 ml/m^2 vs. 43 ± 24 ml/m^2; p = 0.327 for LV end-systolic volume, 43 ± 15% vs. 47 ± 16%; p = 0.367 for LV ejection fraction) (Fig. 1). Of the 30 patients, only 14 (47%) showed a ≥15% decrease in LV end-systolic volume and were regarded as the functional responder to steroid treatment, indicating that the resolution of active myocardial inflammation evaluated by ^{67}Ga scintigraphy or ^{18}F-FDG PET was not linked to the functional responder to steroid treatment. Fig. 2 and Fig. 3 show ^{67}Ga scintigraphy and echocardiography in the functional responder and the non-responder, respectively.

Multivariate analysis revealed that high-degree heart block (odds ratio [OR], 13.5; 95% confidence interval [CI], 1.92–279: p = 0.007) and female gender (OR, 16.0; 95% CI, 1.92–389; p = 0.008) were independently associated with the functional responder to steroid treatment (Table 2). The initial and maintenance doses of prednisone and the period of initial doses of prednisone were not different between the functional responder and the non-responder.

A few studies suggest that steroid treatment is preferable to patients with preserved LV function prior to the irreversible myocardial fibrosis

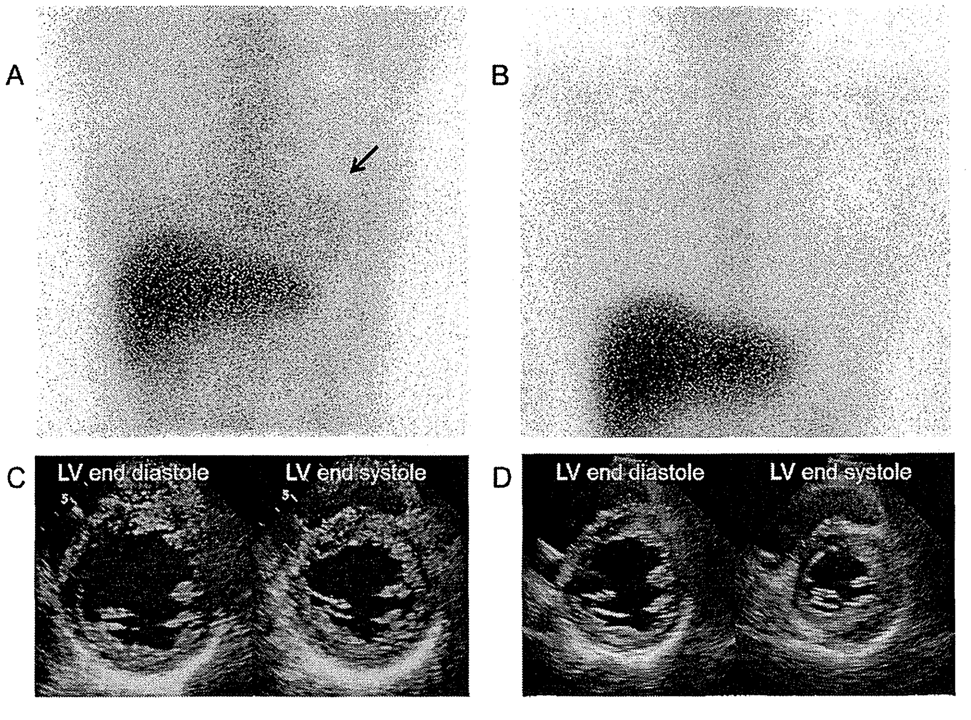

Fig. 2. A 53-year-old woman in whom positive myocardial uptake of ^{67}Ga disappeared after steroid treatment (A,B) and LV function improved (C,D). ^{67}Ga, gallium-67 citrate; LV, left ventricular.

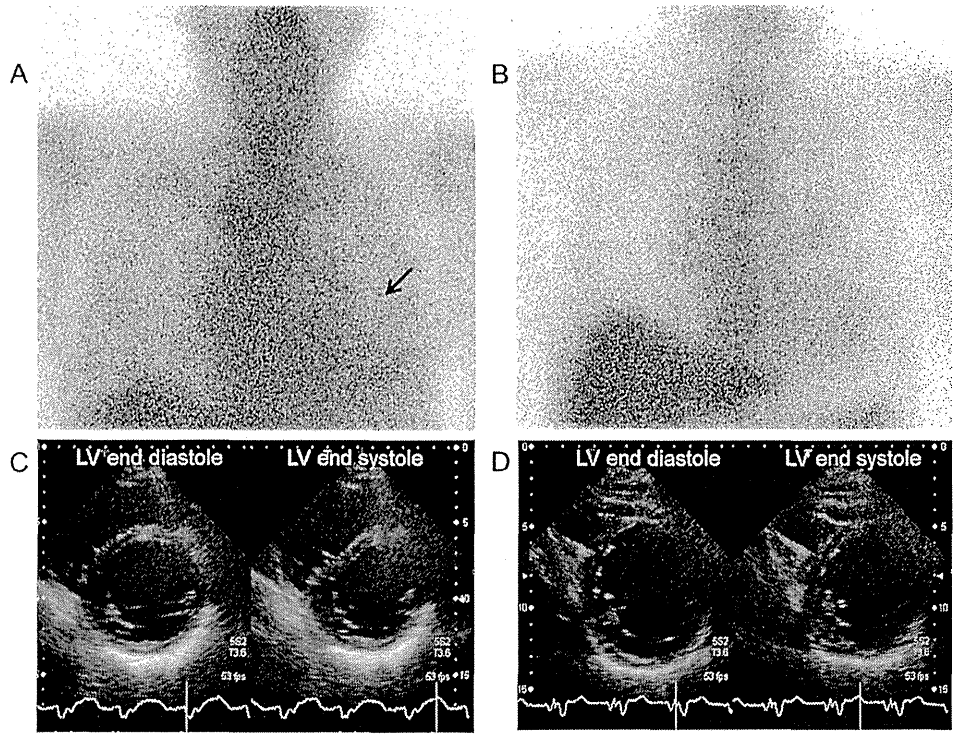

Fig. 3. A 56-year-old man in whom positive myocardial uptake of ^{67}Ga disappeared after steroid treatment (A,B) but LV function did not improve (C,D). ^{67}Ga, gallium-67 citrate; LV, left ventricular.

caused by inflammation [2,3]. The resolution of active myocardial inflammation evaluated by ^{67}Ga scintigraphy or ^{18}F-FDG PET is considered to be a surrogate goal of steroid treatment [4,5]. However, the relationship of anti-inflammation effect of steroid treatment with functional outcome remains unknown. This is the first study to demonstrate that the resolution of active myocardial inflammation by steroid treatment is not linked to the functional responder to steroid treatment. There are possible reasons for the discrepancy. First, the myocardial pathology is a combination of inflammation, fibrosis, and scar. In cases of advanced fibrosis and scar, the functional response may be minimal. Second, we cannot quantify the extent and severity of active myocardial inflammation, which may be related to the functional response. Third, even though positive myocardial uptake of ^{67}Ga or ^{18}F-FDG disappears, active inflammation that cannot be detected by these imaging modalities may be present microscopically.

Table 2
Univariate and multivariate analyses of predicting the functional responder to steroid treatment.

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p	OR (95% CI)	p
Age <65 years	0.33 (0.07–1.51)	0.155		
Female	6.00 (1.14–47.2)	0.033	16.0 (1.92–389)	0.008
NYHA functional class III or IV	1.22 (0.26–5.76)	0.796		
LV ejection fraction <50%	1.14 (0.23–5.76)	0.873		
High-degree heart block	5.40 (1.19–29.0)	0.028	13.5 (1.92–279)	0.007
Beta-blocker use	1.50 (0.33–7.47)	0.604		
Cardiac resynchronization therapy	1.73 (0.32–10.6)	0.526		

OR, odds ratio; CI, confidence interval; NYHA, New York Heart Association; LV, left ventricular.

A unique finding of this study is that high-degree heart block and female gender were associated with the functional responder to steroid treatment. High-degree heart block is caused by inflammation involving the conduction systems. Patients presenting with high-degree heart block as the manifestation of cardiac sarcoidosis may be diagnosed in the phase of disease activity, when steroid treatment is expected to be effective [9]. The reason for gender difference is beyond the scope of the present study.

The main limitation of this study is the small number of patients and lack of a control group that is not treated with prednisone. Another limitation is that we cannot quantity the extent and severity of positive myocardial uptake of ^{67}Ga or ^{18}F-FDG.

In conclusion, steroid treatment is effective for resolving active myocardial inflammation evaluated by ^{67}Ga scintigraphy or ^{18}F-FDG PET, but only about half of them are the functional responders to steroid treatment. The functional responder may be linked to high-degree heart block and female gender but not the resolution of active myocardial inflammation.

Conflict of interest

We have no relationships that could be construed as a conflict of interest.

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Electrocardiographic Parameters and Fatal Arrhythmic Events in Patients With Brugada Syndrome

Combination of Depolarization and Repolarization Abnormalities

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Objectives This study aimed to determine the usefulness of the combination of several electrocardiographic markers on risk assessment of ventricular fibrillation (VF) in patients with Brugada syndrome (BrS).

Background Detection of high-/low-risk BrS patients using a noninvasive method is an important issue in the clinical setting. Several electrocardiographic markers related to depolarization and repolarization abnormalities have been reported, but the relationship and usefulness of these parameters in VF events are unclear.

Methods Baseline characteristics of 246 consecutive patients (236 men; mean age, 47.6 ± 13.6 years) with a Brugada-type electrocardiogram, including 13 patients with a history of VF and 40 patients with a history of syncope episodes, were retrospectively analyzed. During the mean follow-up period of 45.1 months, VF in 23 patients and sudden cardiac death (SCD) in 1 patient were observed. Clinical/genetic and electrocardiographic parameters were compared with VF/SCD events.

Results On univariate analysis, a history of VF and syncope episodes, paroxysmal atrial fibrillation, spontaneous type 1 pattern in the precordial leads, and electrocardiographic markers of depolarization abnormalities (QRS duration ≥120 ms, and fragmented QRS [f-QRS]) and those of repolarization abnormalities (inferolateral early repolarization [ER] pattern and QT prolongation) were associated with later cardiac events. On multivariable analysis, a history of VF and syncope episodes, inferolateral ER pattern, and f-QRS were independent predictors of documented VF and SCD (odds ratios: 19.61, 28.57, 2.87, and 5.21, respectively; $p < 0.05$). Kaplan-Meier curves showed that the presence/absence of inferolateral ER and f-QRS predicted a worse/better prognosis (log-rank test, $p < 0.01$).

Conclusions The combination of depolarization and repolarization abnormalities in BrS is associated with later VF events. The combination of these abnormalities is useful for detecting high- and low-risk BrS patients. (J Am Coll Cardiol 2014;63:2131–8) © 2014 by the American College of Cardiology Foundation

Brugada syndrome (BrS) is a distinct form of idiopathic ventricular fibrillation (VF). BrS is characterized by a unique electrocardiographic pattern consisting of a right bundle branch blocklike morphology and ST-segment elevation in precordial leads. Results of many studies (1–10) have suggested that patients with syncope, particularly patients with a spontaneous type 1 electrocardiographic pattern, have a significant risk of sudden cardiac death (SCD) or VF.

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In the remaining population of asymptomatic subjects, the risk is lower, but not negligible (1,5). Therefore, assessment of the risk of SCD and VF in patients with a Brugada-type electrocardiogram (ECG) is clinically important, especially when sporadic cases are detected during routine medical checkups.

Many markers for the development of VF in BrS have been reported, including clinical markers of a family history

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